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# PENN Clinical Manual of Urology

*Second Edition*

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Thomas J. Guzzo
S. Bruce Malkowicz
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## *Second Edition*

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PENN CLINICAL MANUAL OF UROLOGY ISBN: 978-1-4557-5359-8

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**Library of Congress Cataloging-in-Publication Data**

Penn clinical manual of urology / [edited by] Philip M. Hanno, Thomas J. Guzzo, S. Bruce Malkowicz, Alan J. Wein. – Second edition.
p. ; cm.
Clinical manual of urology
Includes bibliographical references and index.
ISBN 978-1-4557-5359-8 (pbk. : alk. paper)
I. Hanno, Philip M., editor of compilation. II. Guzzo, Thomas J., editor of compilation. III. Malkowicz, S. Bruce, editor of compilation. IV. Wein, Alan J., editor of compilation. V. Title: Clinical manual of urology.
[DNLM: 1. Female Urogenital Diseases. 2. Male Urogenital Diseases. 3. Urology–methods. WJ 100]
RC872.9
616.6–dc23 2013037152

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Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

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To our families, who cheerfully suffer us daily, and to all our residents, past and present, who represent a never-ending source of knowledge, intellectual honesty, and pride

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# PREFACE

Twenty-seven years ago we first put together a basic urology text designed for the busy student and house officer studying this fascinating and evolving area of medicine and surgery. This edition of the *Penn Clinical Manual of Urology* reflects our latest effort to present a useful introductory text. Rather than provide a heavily referenced compendium, we have striven to present a framework upon which program directors can build an educational foundation that will reflect their individual practices and allow their methods to be placed in the perspective of the urologic field in general. We believe the book also will appeal to nonurologic providers who routinely see patients with urologic problems: the primary care physician, gynecologist, nurse practitioner, and urologic nurse specialist. For those studying for certification and recertification in urology, it will be a useful, compact source of information that spans the discipline.

Each of the contributors has been carefully selected, and all are superb clinicians and educators with practical experience in teaching medical students and residents didactically and in the clinic and operating room. All have been affiliated with the Penn urology program, hence the designation of the text. Although the practices and philosophy of the University of Pennsylvania Division of Urology will no doubt be evident in the exposition, more so in some sections than others, we have tried to keep "dogma" to a minimum, and thus allow program directors to add their input without the intellectual disruption (to the reader) of major disagreements. Algorithms, suggested readings, clinical "pearls", and self-assessment questions are a part of each chapter.

From the physical examination to the MR urogram, and from the identification and treatment of testicular torsion to screening for prostate cancer and robotic prostatectomy, we have tried to encapsulate this fast-moving field. Urology incorporates a blend of medicine and surgery, traditional and extremely high-tech procedures, and acute care and long-term follow-up. Our goal has been to present the material in such a way that it will be comprehended by the novice, but also comprehensive enough for the

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chief resident doing a quick board review. It is our hope that this text will find a place not only on the office desk, but also on the clinic bookshelf and in the house staff coat pocket.

We thank our contributors and our publisher for making this edition possible. We hope the *Penn Manual* will prove to be a trusted resource and ready reference.

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## CHAPTER 1

# Signs and Symptoms: The Initial Examination

Keith N. Van Arsdalen, MD

## Background

### DEFINITION

Urology is a surgical specialty devoted to the study and treatment of disorders of the genitourinary tract of the male and the urinary tract of the female. The urologist surgically corrects acquired and congenital abnormalities and diagnoses and treats many medical disorders of the genitourinary tract.

### IMPORTANCE TO OTHER BRANCHES OF MEDICINE

1. Approximately 15% of patients initially presenting to a physician will have a urologic complaint or abnormality.
2. There is a wide overlap with other specialties, and urologists have frequent interaction with other physicians, including family practitioners, internists, pediatricians, geriatricians, endocrinologists, nephrologists, neurologists, obstetricians and gynecologists, and general, vascular, and trauma surgeons.
3. It is important that all physicians be aware of the specific diagnostic and therapeutic measures that are available within this specialty.

## Urologic Manifestations of Disease

### DIRECT

The most obvious manifestations of urologic disease are those signs and symptoms that are directly related to the urinary tract of the male and female or to the genitalia of the male. Hematuria and scrotal swelling are examples in this category.

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## REFERRED MANIFESTATIONS

1. Symptoms from the genitourinary tract may be referred to other areas within the genitourinary tract or to contiguous organ systems.
   a. A stone in the kidney or upper ureter may produce ipsilateral testicular pain.
   b. This same stone may be associated with symptoms of nausea and vomiting.
   c. **The gastrointestinal (GI) tract is probably the most common site to manifest symptoms from primary urologic problems.** This is most probably due to the common innervation of these systems and the close direct relationship between the various component organs.
2. Primary urologic disorders may also be manifest in different organ systems and by seemingly unrelated signs and symptoms. Bone pain and pathologic fractures secondary to metastatic carcinoma arising in the genitourinary tract are examples.
3. Similarly, primary disease in other organ systems may result in secondary urologic signs and symptoms that initially lead the patient to the urologist. Diabetes may be detected by finding glucosuria in a patient presenting with frequency and nocturia. Other signs and symptoms mimicking urologic disease are related to inflammatory or neoplastic processes arising in the:
   a. Lower lobes of the lungs
   b. GI tract
   c. Female internal genitalia

## SYSTEMIC

Fever, weight loss, and malaise can be nonspecific systemic manifestations of acute and chronic inflammatory disorders, renal failure, and genitourinary carcinoma with or without metastases.

## ASYMPTOMATIC

Localized or extensive disease may exist within the genitourinary tract without any signs or symptoms being manifest.

1. Renal calculi or neoplasms may be found during other examinations. **Up to 60% of renal masses are detected incidentally.**

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2. Sixty percent of prostate cancers are detected secondary to prostate-specific antigen (PSA) elevations only without palpable abnormalities of the prostate.
3. Far-advanced renal deterioration may occur prior to the detection of silent reflux or obstruction.

## History

### SYMPTOMS

1. A symptom is any departure from normal appearance, function, or sensation as experienced by the patient. Symptoms are reported to the physician or uncovered by careful history taking, with varying degrees of importance and/or significance attached to each symptom by both parties.
   a. The chief complaint, history of the present illness, and past medical history are delineated in a standard fashion.
   b. The character, onset, duration, and progression of the symptom are carefully defined. It is important to note what factors exacerbate or ameliorate the problem.
2. Urologic symptoms are generally related to:
   a. Pain and discomfort
   b. Alterations of micturition
   c. Changes in the gross appearance of the urine
   d. Abnormal appearance and/or function of the external genitalia

### PAIN

1. Pain within the genitourinary tract generally arises from distention or inflammation of a part or parts of the genitourinary system. Pain can be experienced directly in the involved organ or referred as noted previously. Referred pain is a relatively common symptom of genitourinary disease.
2. Renal pain
   a. The kidney and its capsule are innervated by sensory fibers traveling to the T10-L1 aspect of the spinal cord.
   b. The etiology of renal pain may be due either to capsular distention or inflammation or to distention of the renal collecting system.
   c. Renal pain can be a dull, aching sensation felt primarily in the area of the costovertebral angle or pain of a sharp,

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  colicky nature felt in the area of the flank, with radiation around the abdomen into the groin and ipsilateral testicle or labium. The latter is due to the common innervation.
  d. The nature of the primary disease process within the kidney often determines the type of sensation that is experienced and depends on the degree and rapidity of capsular and/or collecting system distention.
3. Ureteral pain
   a. The upper ureter is innervated in a similar fashion to that for the kidney. Therefore upper ureteral pain has a similar distribution to that of renal pain.
   b. The lower ureter, however, sends sensory fibers to the cord through ganglia subserving the major pelvic organs. Therefore pain derived from the lower ureter is generally felt in the suprapubic area, bladder, penis, or urethra.
   c. The most common etiologic mechanism for ureteral pain is sudden obstruction and ureteral distention.
   d. Acute renal and ureteral colic are among the most severe types of pain known to humankind.
4. Bladder pain
   a. Pain within the bladder may be derived from retention of urine with overdistention or from inflammatory processes.
   b. The pain of overdistention is generally felt within the suprapubic area, resulting in severe local discomfort.
   c. The pain due to bladder inflammation is generally felt as a sharp, burning pain that is often referred to the tip of the penile urethra in males and the entire urethra in females.
5. Prostate pain
   a. Sensory fibers from the prostate mostly enter the sacral aspect of the spinal cord.
   b. Prostate pain is most commonly due to acute inflammation and is generally perceived as discomfort in the lower back, rectum, and perineum.
   c. Irritative symptoms arising from the bladder may overshadow the purely prostate symptoms.
6. Penile pain
   a. Penile and urethral pain are generally directly related to a site of inflammation.
7. Scrotal pain
   a. Pain within the scrotum generally arises from disorders of the testis and/or epididymis.

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   b. The most common etiologic factors include trauma, torsion of the spermatic cord, torsion of the appendix testis or appendix epididymis, and acute inflammation, particularly epididymitis. The pain in these cases is generally of rapid onset, if not sudden, and severe in nature.
   c. Hydroceles, varicoceles, and testicular tumors can also be associated with scrotal discomfort but are generally of a more insidious nature and less severe in most cases.

## ALTERATIONS OF MICTURITION

1. Definitions and problems
   a. Specific terms have been developed to describe alterations related to the act of micturition. This section defines a variety of these terms.
   b. It must be emphasized that a variety of disease processes can result in similar symptoms at the level of the lower urinary tract, and although these terms are used to describe specific symptoms in this area, they do not necessarily pertain to specific etiologies.
2. Changes in urine volume
   a. ***Anuria* and *oliguria* are terms that refer to the varying degrees of decreased urinary output that may be secondary to prerenal, renal, or postrenal factors.** In all cases, it is essential to rule out urethral and/or ureteral obstruction as postrenal causes for these problems.
   b. ***Polyuria* refers to an increase in the volume of urine excreted on a daily basis.** The etiologic mechanisms include increased fluid intake, exogenous or endogenous diuretics, and abnormal states of central or peripheral osmoregulation.
3. Irritative symptoms
   a. *Dysuria* is a term that refers simply to painful or difficult urination. The burning sensation that occurs during micturition associated with either bladder, urethral, or prostatic inflammation is generally used synonymously. This discomfort is generally felt in the entire urethra in females and in the distal urethra in males.
   b. *Strangury* is a subtype of dysuria in which intense discomfort accompanies frequent voiding of small amounts of urine.
   c. *Frequency* refers to the increased number of times one feels the need to urinate. This can be secondary to a true decrease

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in bladder capacity from a loss of elasticity or edema due to inflammation, or it can be secondary to a decrease in the effective bladder capacity due to a failure of the bladder to empty completely with persistence of a large amount of residual urine.

  d. *Nocturia* is essentially the nighttime equivalent of urinary frequency, that is, a decreased real or effective bladder capacity forces the patient to arise at night to urinate.
  e. ***Nycturia* refers to the excretion of larger volumes of urine at night than during the day and is secondary to mobilization of dependent fluid that accumulated when the patient was in the upright position.** Nycturia can result in nocturia even in the presence of a normal bladder capacity if large quantities of fluid are mobilized.
  f. *Urgency* refers to the sudden, severe urge to void that may or may not be controllable.
  g. The irritative symptoms noted previously are most commonly associated with inflammation of the lower urinary tract, that is, bladder and prostate. Acute bacterial infections probably represent the most common etiologic mechanism. It should be noted, however, that the irritative symptoms may be secondary to the presence of a foreign body, nonspecific inflammation, radiation therapy or chemotherapy, neoplasms, and neurogenic bladder dysfunction.
  h. The term *overactive bladder* refers to the symptoms of frequency and urgency, with or without urge or reflex incontinence, in the absence of local pathologic or metabolic factors that would account for these symptoms. The urodynamic-based definition of overactive bladder requires the demonstration of involuntary bladder contractions.

4. Bladder outlet obstructive symptoms
  a. *Hesitancy* refers to the prolonged interval necessary to voluntarily initiate the urinary stream.
  b. *Straining* refers to the need to increase intraabdominal pressure to initiate voiding.
  c. *Decreased force* and *caliber* of the urinary stream refer to the physical changes of the urinary stream that may be noted due to increased urethral resistance.
  d. *Terminal dribbling* refers to the prolonged dribbling of urine from the meatus after the completion of micturition.

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- e. *Sense of residual urine* is the complaint of a sensation of incomplete emptying of the bladder that the patient recognizes after micturition.
- f. *Prostatism.* All of the previous symptoms may be noted with any type of bladder outlet obstruction, that is, secondary to benign prostatic hypertrophy (BPH), prostate carcinoma, or urethral stricture disease. The most common cause of these symptoms, however, is benign prostatic enlargement, and hence this complex of symptoms has often been referred to as *prostatism*.
- g. *Urinary retention.* Acute urinary retention may be associated with severe suprapubic discomfort. Alternatively, the chronic retention of urine within the bladder may occur on a gradual basis due to progressive obstruction and bladder decompensation, and large amounts of urine may be retained with minor changes in symptomatology.
- h. *Interruption* of the urinary stream. Sudden painful interruption of the urinary stream can be secondary to the presence of a bladder calculus that ball valves into the bladder neck, causing abrupt blockage of the urinary flow.
- i. *Bifurcation* of the urinary stream. The symptom of a double stream or spraying of the urinary stream can be secondary to urethral stricture disease or can occur intermittently without any obvious pathology.

5. Incontinence
   - a. *True* or *total incontinence* occurs when constant dribbling of urine comes from the bladder. It may be due to the configuration of the bladder, such as with extrophy or epispadias, to ectopia of the ureteral orifices distal to the bladder neck in females, or to a fistula, usually between the bladder and the vagina. The most common cause, however, is secondary to injury to the sphincter mechanisms of the bladder neck and urethra due to trauma, surgery, or childbirth. Neurogenic disorders affecting the bladder outlet can also have similar effects.
   - b. *False* or *overflow incontinence* is seen with total bladder decompensation in which the bladder acts as a fixed reservoir and the only outflow of urine is an overflow phenomenon with constant dribbling through the bladder outlet.
   - c. *Urgency incontinence* results when the sensation of urgency becomes so severe that involuntary bladder emptying occurs. This is commonly secondary to severe inflammation of the

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urinary bladder. This type of incontinence can also be due to involuntary bladder contractions without inflammation (see definition of overactive bladder on Page 6).

   d. *Stress incontinence* is secondary to distortion of the normal anatomic relationship between the bladder and the urethra such that sudden increases in intraabdominal pressure (laughing, straining) are transmitted unequally to the bladder and the urethra, resulting in elevated bladder pressure without a concomitant rise in urethral pressure. Most commonly, this is related to laxity of the pelvic floor, particularly following childbirth, but it may also be noted in women who have not had children. It is also a frequent sequel of radical prostatectomy surgery for prostate cancer.
   e. **It is important to differentiate the various types of incontinence because each is treated differently. Historical factors are very important in separating these different entities.**

6. *Enuresis* refers to involuntary urination and bed-wetting that occurs during sleep.
7. Quantification of voiding symptoms
   a. **The AUA Symptom Index (internationally known as the IPSS) is a self-administered questionnaire consisting of seven questions relating to symptoms of lower urinary tract voiding dysfunction (Table 1-1).** The IPSS includes a quality-of-life question to assess the degree of bother experienced by the patient.
   b. Symptoms are classified as mild (0-7), moderate (8-19), or severe (20-35).
   c. The symptom score is an integral part of the clinical practice guidelines for treatment planning and follow-up for BPH management.
   d. The symptom score is not specific for or diagnostic of BPH. It can be used in men and women for general assessment of voiding symptoms.

## CHANGES IN THE GROSS APPEARANCE OF THE URINE

1. Cloudy urine
   a. Cloudy urine is most commonly due to the benign process of precipitation of phosphates in an alkaline urine (phosphaturia). This may be noted after meals or after consumption of large quantities of milk and is generally

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TABLE 1-1 **The AUA Symptom Index**

| Question | Not at All | Less Than 1 Time in 5 | Less Than Half the Time | About Half the Time | More Than Half the Time | Almost Always |
|---|---|---|---|---|---|---|
| 1. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. During the last month or so, how often have you had to urinate again less than 2 hours after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. During the last month or so, how often have you found you stopped and started again several times when you urinated? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. During the last month or so, how often have you found it difficult to postpone urination? | 0 | 1 | 2 | 3 | 4 | 5 |

*(Continued)*

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TABLE 1-1 **The AUA Symptom Index—Cont'd**

| Question | Not at All | Less Than 1 Time in 5 | Less Than Half the Time | About Half the Time | More Than Half the Time | Almost Always |
|---|---|---|---|---|---|---|
| 5. During the last month or so, how often have you had a weak urinary stream? | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. During the last month or so, how often have you had to push or strain to begin urination? | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? | None<br>0 | 1 time<br>1 | 2 times<br>2 | 3 times<br>3 | 4 times<br>4 | 5 or more times<br>5 |
| AUA symptoms score = sum of questions 1 to 7. | | | | | | |

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intermittent in nature. Patients are otherwise asymptomatic. Acidification of the urine with acetic acid at the time of urinalysis causes prompt clearing of the specimen.

   b. *Pyuria* refers to the finding of large quantities of white blood cells that cause urine to have a cloudy appearance. Microscopic examination of the urine sample will demonstrate the inflammatory nature that is usually secondary to an infection.
   c. *Chyluria* refers to the presence of lymph fluid mixed with the urine. It is an unusual cause of cloudy urine.

2. *Pneumaturia* refers to the passage of gas along with urine while voiding. There may be associated pyuria or frank fecal contamination of the urine, as this phenomenon is almost exclusively due to the presence of a fistula between the GI and urinary tracts. On occasion, the presence of a gas-forming infection within the urinary tract can produce similar symptoms, although this is very unusual.
3. Hematuria
   a. The passage of bloody urine is always alarming, and generally the patient makes a prompt visit to the physician. Investigation is always warranted, including a properly performed urinalysis to be certain that the red discoloration of the urine is indeed secondary to the presence of blood. For a differential diagnosis of the causes of red urine, see Page 12.
   b. Although hematuria is always a danger signal, a clue to its significance may lie in whether there is associated pain or whether the bleeding is essentially painless. Pain that occurs in association with cystitis or passage of a urinary tract calculus may indicate that the bleeding is in fact benign in nature. **Painless hematuria, however, is always believed to be secondary to a urinary tract neoplasm until proven otherwise.** This differentiation is not infallible, and therefore all urinary tract bleeding warrants investigation to be certain that there is not an associated neoplasm in addition to the more obvious cause for painful bleeding.
   c. The probable site of bleeding within the urinary tract may be ascertained by determining whether the bleeding is initial (at the beginning of the stream only), terminal (at the end of the stream only), or total (throughout the entire stream).

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Initial hematuria generally indicates some type of anterior urethral bleeding that is flushed out by the initial passage of the bladder urine through the urethra. Terminal hematuria is often secondary to posterior urethral, bladder neck, or trigone bleeding and is noted when the bladder finally compresses these areas at the end of micturition. Total hematuria indicates that the bleeding occurs at the level of the bladder or above, such that all of the urine is mixed with blood and is therefore bloody throughout the entire stream.

4. *Colored urine* may result from a variety of foods, medications, and medical disorders. The colors may range from almost clear to black, with all other colors of the spectrum noted in between. (See Table 1-2 for common causes of colorful urine.)

## ABNORMAL APPEARANCE AND FUNCTION OF THE MALE EXTERNAL GENITALIA

1. Sexual dysfunction
2. Infertility
3. Penile problems
    a. *Cutaneous lesions.* A variety of exophytic and ulcerative lesions may be noted by the patient. The relationship of the onset of these lesions to recent sexual activity should be explored. The physical characteristics of these lesions should be noted at the time of physical examination. The combination of historical and physical factors and associated physical findings such as adenopathy will provide a working diagnosis for the treatment of these lesions.
    b. *Penile curvature.* Bending of the penis, particularly during erection, is noted in association with scarring and fibrosis of the tunica albuginea. These plaque-like structures may be noted on physical examination. The process is essentially idiopathic and has been referred to as *Peyronie disease*. Congenital curvature is usually in a ventral direction and is not associated with fibrosis or formation of a plaque.
    c. *Urethral discharge.* The character of the urethral discharge and its onset in relation to sexual activity should be described. The presence of the discharge should be confirmed on physical examination, a microscopic examination performed, and a culture obtained.

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TABLE 1-2 **Common Causes of Colorful Urine**

| | |
|---|---|
| Colorless | Very dilute urine |
| | Overhydration |
| Cloudy/milky | Phosphaturia |
| | Pyuria |
| | Chyluria |
| Red | Hematuria |
| | Hemoglobin/myoglobinuria |
| | Anthocyanin in beets and blackberries |
| | Chronic lead and mercury poisoning |
| | Phenolphthalein (in bowel evacuants) |
| | Phenothiazines (Compazine, etc.) |
| | Rifampin |
| Orange | Dehydration |
| | Phenazopyridine (Pyridium) |
| | Sulfasalazine (Azulfidine) |
| Yellow | Normal |
| | Phenacetin |
| | Riboflavin |
| Green-blue | Biliverdin |
| | Indicanuria (tryptophan indole metabolites) |
| | Amitriptyline (Elavil) |
| | Indigo carmine |
| | Methylene blue |
| | Phenols (IV cimetidine [Tagamet], IV promethazine [Phenergan], etc.) |
| | Resorcinol |
| | Triamterene (Dyrenium) |
| Brown | Urobilinogen |
| | Porphyria |
| | Aloe, fava beans, and rhubarb |
| | Chloroquine and primaquine |
| | Furazolidone (Furoxone) |
| | Metronidazole (Flagyl) |
| | Nitrofurantoin (Furadantin) |
| Brown-black | Alcaptonuria (homogentisic acid) |
| | Hemorrhage |
| | Melanin |
| | Tyrosinosis (hydroxyphenylpyruvic acid) |
| | Cascara, senna (laxatives) |
| | Methocarbamol (Robaxin) |
| | Methyldopa (Aldomet) |
| | Sorbitol |

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  d. *Bloody ejaculate*. Like hematuria, this is also a frightening experience that usually causes the patient to seek prompt attention. This problem, however, is generally secondary to benign congestion and/or inflammation of the seminal vesicles. The process is usually self-limited or treatable with antibiotics and does not initially require an extensive evaluation.

4. Scrotal problems
  a. *Cutaneous lesions*. The hair-bearing skin of the scrotum is susceptible to skin diseases that can occur anywhere else on the body. Fungal infections and venereal warts may also be noted commonly.
  b. *Scrotal swelling* and *masses*. The presence of scrotal swelling and/or a scrotal mass may be noted incidentally by the patient while bathing or performing a self-examination or due to the presence of associated discomfort. A variety of lesions can produce unilateral or bilateral scrotal enlargement. These range from normal structures that are misinterpreted by the patient to testicular neoplasms. The differential diagnosis is as noted in the box below. A combination of historical information, particularly with regard to onset of the mass, progression, and associated pain, and the physical examination is helpful in differentiating some of the more confusing lesions.

**DIFFERENTIAL DIAGNOSIS**

***Scrotal Swelling***

| **Structure Involved** | **Pathology** |
|---|---|
| Scrotal wall | Hematoma<br>Urinary extravasation<br>Edema from cardiac, hepatic, or renal failure |
| Testis | Carcinoma<br>Torsion of testes or appendix testis |
| Epididymis | Epididymitis<br>Tumor<br>Torsion of appendix epididymis |
| Spermatic cord | Hydrocele surrounding testis of involving cord only<br>Hematocele<br>Hernia<br>Varicocele<br>Lipoma |

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## The Physical Examination

### GENERAL INFORMATION

1. The problems delineated in the history will determine how extensive the physical examination should be. A complete physical examination is obviously necessary for someone who will undergo some type of urologic surgery; in most instances, however, a limited examination of the genitourinary tract is usually sufficient at the time of the initial examination.
2. The commonly taught techniques of physical examination, including inspection, palpation, percussion, and auscultation, are also used during the urologic examination. Each has varying degrees of usefulness, depending on the organ being evaluated. Particular aspects of the physical examination will be noted later.

### KIDNEYS AND FLANKS

1. *Inspection.* Inspection of the flanks is best carried out with the patient in the sitting or standing position facing straight ahead and the examiner located behind the patient facing the area in question. Scoliosis may be evident in the patient with an inflammatory process directly or indirectly involving the psoas muscle with resultant spasm. Bulging of the flank may be noted if an underlying mass exists, although this is evident in most cases only if the mass is extremely large or the patient is very thin. Edema of the flank may be noted if there is an underlying inflammatory process.
2. *Palpation* and *percussion.* A method of bimanual renal palpation has been described with the patient in the supine position (Figure 1-1). The examiner lifts the flank by placing one hand beneath this area and subsequently palpates deeply beneath the ipsilateral costal margin anteriorly. This technique is successful in children and thin adults but generally yields little information under most other circumstances. A large mass may be palpable. Percussion is a useful technique, particularly in the area of the costovertebral angle, to elicit tenderness due to underlying capsular inflammation or distention (Figure 1-2).
3. *Auscultation.* This technique is particularly useful in evaluating patients with possible renovascular hypertension. An underlying

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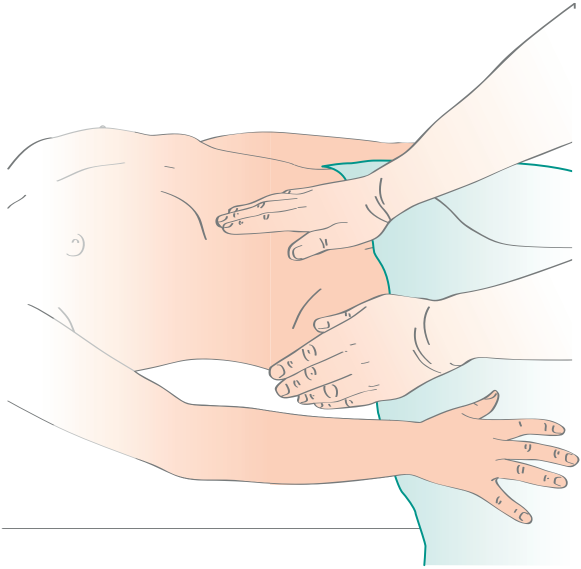

**FIGURE 1-1** With the patient in the supine position, one hand is used to raise the flank while the abdominal hand palpates deeply beneath the costal margin. (From Van Arsdalen K: Signs and symptoms: The initial examination. In Hanno P, et al: *Clinical manual of urology,* New York, 2001, McGraw-Hill, Fig. 2-1.)

bruit may be noted in the area of the costovertebral angle due to renal artery stenosis, aneurysm formation, or arteriovenous malformation.

4. *Transillumination.* This technique, which may differentiate a solid from a cystic mass in neonates or infants, has largely been replaced by ultrasonography, which defines these lesions much more clearly.

## ABDOMEN AND BLADDER

1. *Inspection.* The abdominal and bladder examinations are best carried out with the patient in the supine position. The full or overdistended bladder may be visible on general inspection of the abdomen with the patient in this position.
2. *Palpation* and *percussion.* It is generally possible to palpate or percuss the bladder above the level of the symphysis pubis if it contains 150 mL or more of urine (Figure 1-3). It should be

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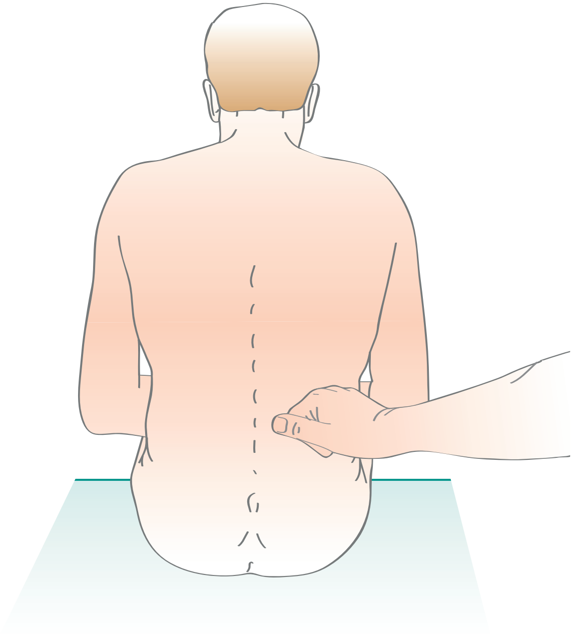

FIGURE 1-2 Gentle percussion with the heel of the hand in the angle between the lumbar vertebrae and the twelfth rib is useful in eliciting underlying tenderness due to obstruction or inflammation. (From Van Arsdalen K: Signs and symptoms: the initial examination. In Hanno P, et al: *Clinical manual of urology.* New York, 2001, McGraw-Hill, Fig. 2-2.)

remembered that in the child, the bladder *may* be percussible or palpable with much smaller volumes of urine due to the fact that it is more of an intraabdominal organ in the child than the true pelvic organ it is in the adult.

## PENIS

1. *Inspection.* Inspection of the penis will reveal obvious lesions of the skin and will define whether the patient has been circumcised. If the patient has been circumcised, the glans penis and meatus can be inspected directly. In the uncircumcised patient, the foreskin, glans, and meatus should then be inspected. The number and position of ulcerative and/or exophytic lesions

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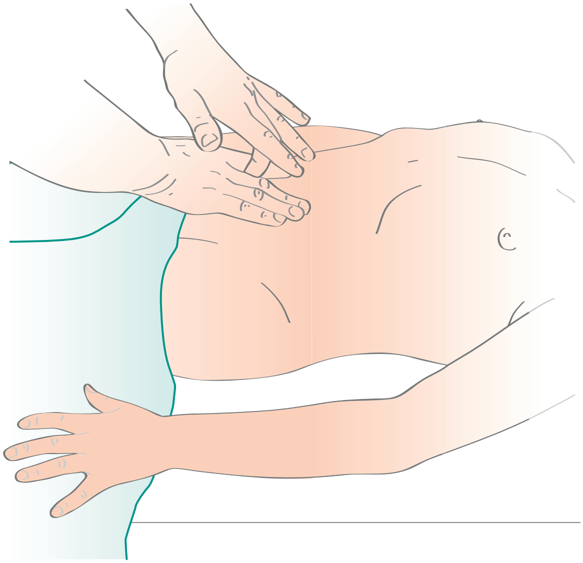

FIGURE 1-3 Percussion over the bladder may be particularly useful when palpation is difficult due either to obesity or failure of the patient to relax during the examination. The bladder may be percussed if it contains greater than 150 mL of urine in the adult. (From Van Arsdalen K: Signs and symptoms: the initial examination. In Hanno P, et al: *Clinical manual of urology*. New York, 2001, McGraw-Hill, Fig. 2-3.)

should be noted if they are present. The position and size of the urinary meatus should be defined.

a. *Foreskin*. Phimosis is present when the orifice of the foreskin is constricted preventing retraction of the foreskin over the glans. Paraphimosis is present when the foreskin, once retracted over the glans, cannot be replaced to its normal position covering the glans.
b. *Penile meatus*. The normal meatus should be located at the tip of the glans. Hypospadias is present when the meatus opens anywhere along the ventral aspect of the penis or in the perineum. Epispadias is present when the meatus is located on the dorsal aspect of the penis.

2. *Palpation*. Palpation of the penile shaft is important to identify and define the limits of areas of fibrous induration that may be found in patients with Peyronie disease who complain of

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penile curvature during erection. The urethra should also be palpated for areas of induration that may be associated with periurethritis and urethral stricture disease. The urethra can also be "stripped" from the penile-scrotal junction toward the meatus to look for a urethral discharge that can then be collected for microscopic examination and culture.

## SCROTUM AND SCROTAL CONTENTS

1. *Inspection.* The inspection of the scrotum and the remainder of this portion of the physical examination are best carried out with the patient initially in the standing position. Lesions of the scrotal skin are readily evident in this position. The examiner also generally notes that if two testicles are present, one usually hangs lower than the other. In most cases, the left testicle is lower than the right. In cases of congenital absence or failure of descent of one or both testicles, the involved side may demonstrate hypoplastic scrotal development. It is always important to note the presence or absence of the testes. Scrotal masses and the "bag of worms" appearance of an underlying large varicocele may be identified on initial inspection.
2. *Palpation.* The contents of each hemiscrotum should be palpated in an orderly fashion. First, the testes should be examined, then the epididymides, then the cord structures, and finally the area of the external inguinal ring to check for the presence of an inguinal hernia (Figure 1-4).
    a. Each testis should be in the dependent portion of the scrotum when the patient is relaxed and in a warm environment. The long axis of the testicle should be in a vertical direction, and the size of the testis should normally be greater than or equal to 4 cm in adult males.
    b. Each epididymis is adherent to the posterolateral aspect of the testicle. The head of the epididymis is noted to be near the superior pole of the testicle, the body of the epididymis is near the middle portion of the testicle, and the tail of the epididymis represents the most inferior aspect of this structure. The examiner should palpate each portion of the epididymis, looking primarily for areas of tenderness or induration.
    c. The spermatic cord varies somewhat in thickness, and often this depends on the presence or absence of what has been termed a *lipoma of the cord*. The examiner should be

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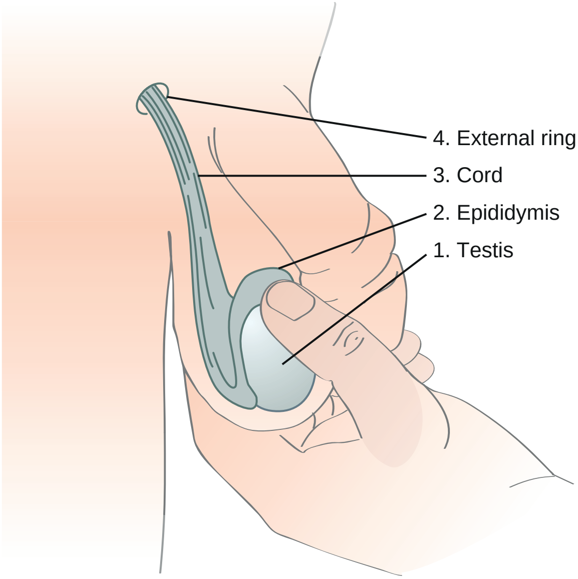

Palpate in sequence: 1. testis 2. epididymis - head, body, tail 3. cord 4. external ring

**FIGURE 1-4 Palpation of the scrotal contents should be carried out in an orderly, routine fashion. One should begin palpating the testes, followed by the epididymides, the cord structures, and finally the external rings. Palpating each structure from side to side is useful for detecting differences in testicular size and identifying varicoceles. All of the scrotal structures may be examined between the thumb and the index and middle fingers.** (From Van Arsdalen K: Signs and symptoms: the initial examination. In Hanno P, et al: *Clinical manual of urology*. New York, 2001, McGraw-Hill, Fig. 2-4.)

particularly attentive to the presence or absence of enlarged venous structures (i.e., a varicocele). If a varicocele is detected, the patient should also be examined in the supine position to be certain that the varicocele decompresses. If it does not, one must suspect inferior vena cava or renal vein obstruction. Changes in the size of the cord between the standing and the supine positions or when using the Valsalva maneuver with the patient in the upright position indicate the presence of a small varicocele. The vas deferens should be palpated. This structure normally has the thickness of a pencil lead and has a distinct, smooth firmness.

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d. Finally, with the patient in the standing position, palpation of the inguinal canal may be carried out. Increasing intraabdominal pressure by asking the patient to cough or by using the Valsalva maneuver will help to define the presence of an inguinal hernia.

3. Abnormal scrotal masses and transillumination (Figures 1-5 and 1-6).
   a. The presence of an abnormal mass within the scrotum is best defined by careful palpation. It should be noted whether the mass arises from the testicle, is contained within the testicle, arises from the epididymis, is located in the cord, or tends to surround most of the scrotal structures. It is important to note the character of the mass, that is, whether it is hard, firm, or cystic in nature.
   b. **All scrotal masses should be transilluminated, and this can be accomplished with a small penlight.** Any mass that radiates a reddish glow of light through the lesion represents a cystic, fluid-filled structure. Caution is advised in defining the benignity of these lesions, however, in that benign and malignant lesions can coexist. A hydrocele surrounding a testicular tumor is an example.
   c. See the box below for a differential diagnosis of scrotal masses.

## DIFFERENTIAL DIAGNOSIS

***Scrotal Discomfort and Solid Mass Lesions***

| | **Torsion** | **Epididymitis** | **Tumor** |
|---|---|---|---|
| **Age** | **Birth to 20 years** | **Puberty to old age** | **15 to 35 years** |
| **Pain** | | | |
| Onset | Sudden | Rapid | Gradual |
| Degree | Severe | Increasing severity | Mild or absent |
| Nausea/vomiting | Yes | No | No |
| **Examination** | | | |
| Testis | Swollen together and both tender | Normal early | Mass |
| Epididymis | | Swollen, tender | Normal |
| Spermatic cord | Shortened | Thickened, often tender as high as inguinal canal | |
| Urinalysis | Normal | Often infection | Normal |

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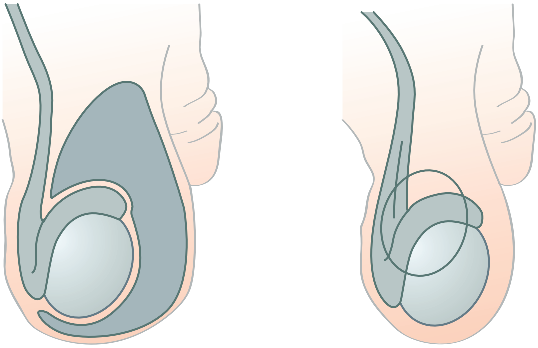
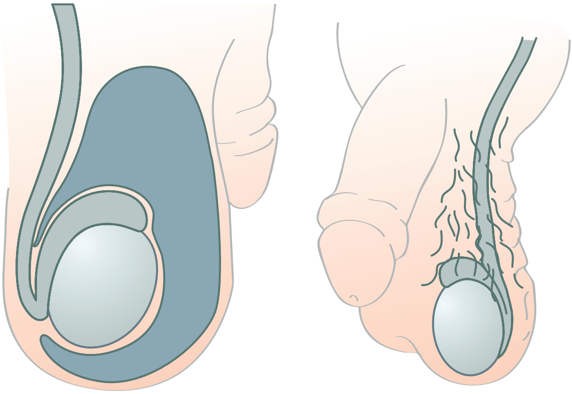


Hydrocele

Spermatocele



Hematocele

Varicocele

FIGURE 1-5 A variety of fluid-filled masses develops within the scrotum. Hydroceles and spermatoceles (and occasionally bowel in the hernia sac) will transilluminate. Hydrocele fluid is contained within the tunica vaginalis and essentially surrounds the testicle. A spermatocele generally occurs above or adjacent to the upper pole of the testis and represents a cyst of the rete testis or epididymis. A hematocele is a collection of blood within the tunica vaginalis due usually to trauma or surgery. Occasionally bleeding will occur spontaneously that is associated with bleeding disorders. A varicocele represents dilated veins of the pampiniform plexus. Hematoceles and varicoceles will not transilluminate. (From Van Arsdalen K: Signs and symptoms: the initial examination. In Hanno P, et al: *Clinical manual of urology.* New York, 2001, McGraw-Hill, Fig. 2-5.)

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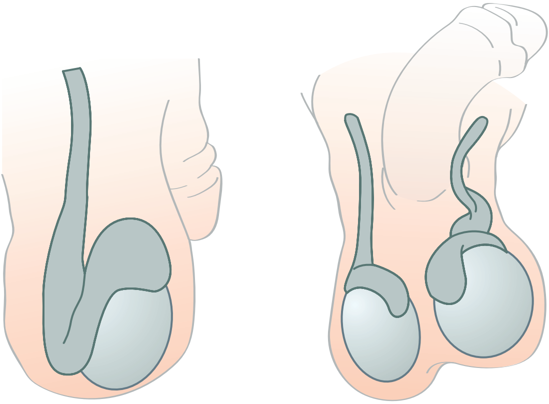
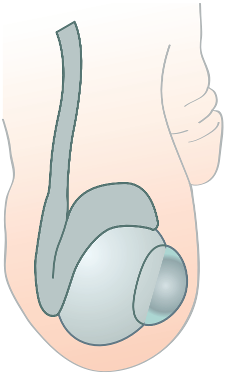


Epididymitis

Testicular torsion



Testicular tumor

FIGURE 1-6 **Solid scrotal masses may be painful or painless and may involve the testis, epididymis, or both.** (From Van Arsdalen K: Signs and symptoms: the initial examination. In Hanno P, et al: *Clinical Manual of Urology.* New York, 2001, McGraw-Hill, Fig. 2-6.)

## THE RECTUM AND PROSTATE

1. *Position.* Various positions have been described for performing a digital rectal examination (DRE). Having the patient lie on the examining table in the lateral decubitus position with the legs flexed at the hips and knees and the uppermost leg pulled higher toward the chest than the lowermost leg creates a comfortable position for the patient and the examiner (Figure 1-7).

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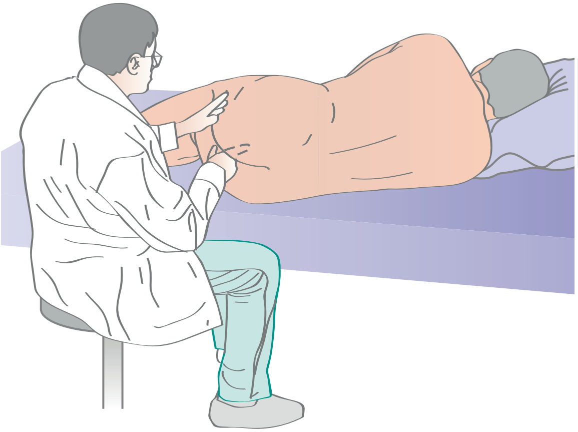
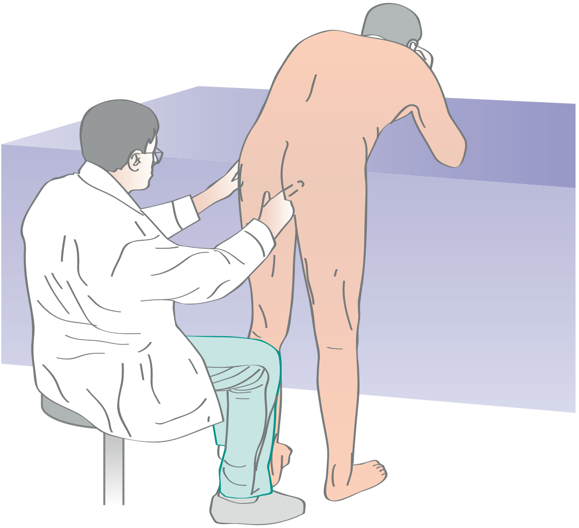


Lying position



Standing position

**FIGURE 1-7 Two positions are illustrated for performing the digital rectal examination (DRE).** (From Van Arsdalen K: Signs and symptoms: the initial examination. In Hanno P, et al: *Clinical manual of urology.* New York, 2001, McGraw-Hill, Fig. 2-7.)

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Alternatively, the patient can bend over the examining table while in the standing position so that the weight of his upper body rests on his elbows. The lateral decubitus position typically allows for deeper penetration of the rectum to feel the prostate in obese patients or to feel the top of large glands. Probably more important than the position, however, is that the gloved examining finger be adequately lubricated and slow, gentle pressure be applied as the finger traverses the anal sphincter. A rectal examination can be an extremely painful or a painless experience, depending on the skill and patience of the examiner. It is important at the time of the examination, not only to palpate the prostate gland, but to palpate the entire inside of the rectum in search of other abnormalities.

2. *Prostate*. During the rectal examination, the posterior aspect of the prostate is palpated (Figure 1-8). The significance of this part of the general physical examination cannot be overemphasized. Most types of prostate carcinoma begin in the posterior lobe of the prostate, which is very accessible to the examining finger.
   a. **The prostate gland is normally a small, walnut-sized structure with a flattened, heart-shaped configuration.** A median furrow runs down the longitudinal axis of the prostate. There are two lateral sulci, where the rectal mucosa folds back on itself after reflecting off the prostate. The consistency of the normal prostate is generally described as "rubbery" in nature and has been likened to the consistency of the thenar eminence when one opposes the thumb and fifth finger.
   b. Abnormal consistency of the prostate may be noted on rectal examination and includes nodular abnormalities that can be raised or within the substance of the prostate, areas of induration that can suggest malignancy, or areas of bogginess or fluctuance that can be associated with abscess formation.
   c. Prostatic massage can be carried out to express prostatic secretions into the urethral lumen. These secretions may then be collected directly if they happen to drain through the penile meatus or by having the patient void a small amount of urine directly into a container immediately

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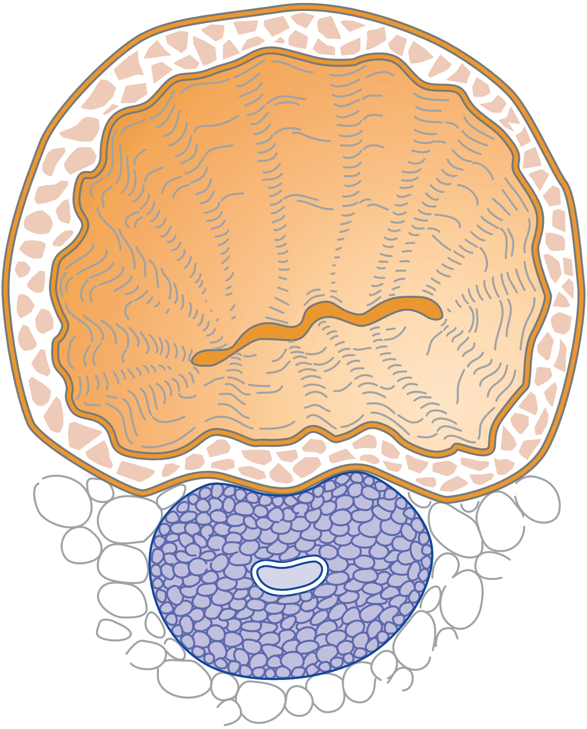

FIGURE 1-8 The posterior aspect of the prostate is palpable on rectal examination. The surface is normally smooth, rubbery, and approximately 4 x 4 cm in size. The median furrow may be lost with diffuse enlargement of the gland, and the lateral sulci may be either accentuated or obscured. Deviations from normal contour, consistency, or size should be carefully described. Stating that an area is "hard" implies the presence of carcinoma. The seminal vesicles are not normally palpable. *Remember:* Check the entire rectum. Do not miss an occult rectal carcinoma. (From Smith DR, *General urology*, ed 11, New York, 1984, McGraw-Hill.)

following the massage. Prostatic massage is generally carried out in a methodical fashion to strip the entire gland from a lateral to a medial aspect bilaterally.

3. *Seminal vesicles.* Under normal conditions, the seminal vesicles are not palpable. They can become evident on a rectal examination, however, if they are enlarged due to obstruction or inflammation.

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### THE VAGINAL EXAMINATION

1. *Inspection*. The vaginal examination is best performed with the patient in the relaxed lithotomy position. Inspection of the vulva may reveal a variety of venereal and nonvenereal lesions. The urinary meatus should be identified and its position and size noted. An erythematous tender lesion arising from the meatus may represent a benign urethral caruncle or possibly a urethral carcinoma. The character of the vaginal mucosa at the introitus should be noted. The examiner *may* also note the presence of a cystocele or a rectocele while examining the patient in this position. These structures may be accentuated with increases in intraabdominal pressure such as those that occur with coughing or straining. In fact, this maneuver may elicit some leakage of urine in patients with stress urinary incontinence.
2. *Palpation*. Palpation of the urethra to the level of the bladder neck and trigone may be accomplished during examination of the anterior vaginal wall. Bimanual palpation is useful to define the internal genitalia and to define further the size and consistency of the urinary bladder.

## The Urinalysis and Culture

### COLLECTION

Proper collection and prompt examination of the urine are essential to gain the most information from the routinely collected specimen.

1. Males
   a. A midstream urine collection is most commonly obtained in men for routine examination. With this technique, the male patient is instructed to retract the foreskin if he is uncircumcised and to gently cleanse the glans. He begins to urinate into the toilet, subsequently inserting a sterile glass container into the urinary stream to collect a urine sample. The container is then removed and the act of voiding is completed.
   b. A variety of other collection techniques affords more information with regard to localization of infection within the urinary tract. Four such specimens may be obtained and analyzed separately by routine microscopic

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evaluation and culture techniques. These have been designated the VB-1, VB-2, EPS, and VB-3 specimens, according to Stamey. The VB-1 is the initial 5 to 10 mL of the stream, which contains bladder urine mixed with urethral contents that are initially washed from the urethra. The VB-2 specimen is essentially the midstream portion of the collection. The EPS specimen represents the expressed prostatic secretions following prostatic massage. Finally, the VB-3 specimen represents a small voided specimen that mixes bladder urine with the contents contained in the urethra immediately following the expression of prostatic secretions. This collection is particularly useful if inadequate amounts of secretion from the prostate are expressed during the prostatic massage. The value of these cultures for localization of urinary tract infection is that the VB-1 represents urethral flora, the VB-2 represents bladder flora, and the EPS and VB-3 represent prostatic flora.

2. Females
   a. The midstream urine collection in females is somewhat more difficult to accomplish and is often considered to be inadequate for even the most routine examination. With this technique, the vulva is cleansed and the stream is initiated into the toilet with subsequent insertion of a collecting container as described previously for the male. If this specimen is grossly contaminated or appears infected, then one of the collection methods noted later may be necessary to differentiate these two possibilities. However, if the collection has been done with reasonable care and the specimen is essentially negative on microscopic examination, then this technique is generally considered adequate.
   b. A more proper method of midstream urine collection has been described in which the patient is placed in the lithotomy position and then asked to void. The nurse holds the labia apart to prevent contamination and collects a midstream specimen. This is often awkward, if not difficult, for both the patient and the nurse, and this method of collection is not recommended.
   c. If there is any question with regard to the problem of contamination versus infection of the midstream specimen

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as noted previously, then catheterization to obtain a true bladder specimen is the preferred technique. An examiner should not hesitate to use this method to properly categorize a patient's problem.

3. Children
   a. Percutaneous suprapubic aspiration of urine from neonates and infants is a particularly useful method of obtaining a truly uncontaminated specimen of urine from the bladder. With this technique, the suprapubic area is cleansed with an antiseptic solution and percutaneous aspiration is performed with a fine-gauge needle. The specimen can then be examined for urinalysis and sent for culture.
   b. A variety of sterile plastic bags is available with adhesive collars that surround the male and female infant's genitalia. They are particularly useful for routine screening urinalysis, but as with the collection of midstream specimens from women, it may be difficult at times to differentiate a truly infected urine specimen from a contaminated one due to this collection technique.
   c. Older boys and girls may have urine collected in a fashion similar to that described previously for their adult counterparts. One is generally quite hesitant, however, to catheterize young boys due to the possibility of urethral trauma. It is easier and safer to perform this in girls and may be used if necessary.

## PHYSICAL ASPECTS OF URINE

1. *Color.* The color of urine is generally a clear, light yellow, but a wide range of colors has been described. The changes in color can be secondary to foods and medications and to intrinsic disease processes. Table 1-2 describes the etiologic factors in relationship to abnormal urine color.
2. *pH.* The normal pH of urine ranges from 4.5 to 8.0. Urine is described as having an acid pH if it ranges between 4.5 and 5.5. It has an alkaline pH if it ranges between 6.5 and 8.0.
3. *Specific gravity.* The specific gravity can be determined in the office by relatively simple techniques and gives some idea of the concentrating ability of the kidneys and their ability to excrete waste products. A variety of substances within the

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urine, such as intravenous contrast material, can detract from the value of this test. The osmolality of the urine is a better indicator of renal function but requires standard laboratory methods.

## DIPSTICK TESTS

1. A variety of dipsticks is available to evaluate the urine sample. These consist of short plastic strips with small pads that are impregnated with a variety of reagents that react with abnormal substances within the urine.
2. In addition to determination of urinary pH, the most sophisticated dipsticks now contain reagents for the determination of the following:
   a. Protein
   b. Glucose
   c. Ketones
   d. Urobilinogen
   e. Bilirubin
   f. Blood
   g. Hemoglobin
   h. Leukocytes
   i. Nitrites

## MICROSCOPIC EXAMINATION

1. A small portion of the collected urine sample is placed in a test tube and centrifuged at approximately 5000 rpm for 5 minutes. The supernate is then poured from the tube, and the remaining sediment is resuspended in the small quantity of urine that drains back down the side of the tube to the sediment. A drop of the resuspended sediment is placed on a glass slide followed by a cover slip.
2. The wet specimen is then examined under low and high power for the presence and number of epithelial cells, red blood cells, white blood cells, bacteria, and casts.

## URINE CULTURE

1. **If a urine culture is desired, it should be promptly plated in the office or sent immediately to the laboratory to prevent overgrowth of bacteria and falsely elevated bacterial counts.**
2. The value of localization cultures has been noted previously.

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## Blood Tests

### PANEL 7 (OR SIMILAR DESIGNATION)

1. Serum electrolytes (Na, K, Cl, $CO_2$) are useful indicators of maintenance of homeostasis for which the kidney plays a significant role.
2. Glucose levels in the serum may be variable relative to the presence of glucosuria.
   a. Diabetes is a significant risk factor for voiding and sexual dysfunction.
3. Blood urea nitrogen (BUN) and creatinine are indicators of renal function.

### PSA LEVEL

1. PSA is a protein kinase produced by the prostatic epithelium.
   a. It is a normal component of the ejaculate responsible for liquification of the semen.
   b. Normally found in very low levels in serum (0-4.0 ng/mL).
2. Causes of PSA elevation
   a. Prostate cancer
   b. BPH
   c. Prostatitis (acute and chronic)
   d. Instrumentation (catheterization, cystoscopy, biopsy)
   e. Urinary retention
   f. Vigorous prostatic massage, probably little elevation for routine DRE
3. PSA as a tumor marker
   a. Limitations due to prostate organ specific but not cancer specific.
   b. Substantial overlap of values for men with prostate cancer and benign conditions.
   c. Absolute value greater than 10 ng/mL has more than 60% predictive risk of prostate cancer.
   d. Sixty percent of current prostate cancer diagnoses are made due to an elevated PSA level.
   e. Useful marker for following efficacy of treatment for prostate cancer.
4. Recommendations
   a. One must be familiar with the guidelines and controversies for prostate cancer screening using PSA levels.

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# Instrumentation

## GENERAL INFORMATION

The instrumentation and procedures can be commonly performed in the office setting under local anesthesia. Some of these techniques, such as cystourethroscopy, placement of retrograde catheters, and biopsy of the prostate, may also be performed with regional or general anesthesia.

## URETHRAL CATHETERS

1. *Straight catheters*. The standard straight, red Robinson catheter is useful for office catheterization when an indwelling catheter is not warranted. It is useful for collecting relatively uncontaminated specimens directly from the bladder as noted previously.
2. *Standard balloon* or *Foley catheter.* This type of catheter has a double lumen that permits drainage of urine through the larger lumen and inflation of a balloon located at the tip of the catheter. This allows it to be retained within the urinary bladder. This type of catheter is useful following certain operative procedures on the urinary tract and for establishing temporary, constant urinary drainage, to monitor urine output, or for relief of bladder outlet obstruction. These catheters generally have 5- and 30-mL balloons, but the amount of water placed in these balloons is not precisely critical because each will hold significantly more than its stated volume.
3. *Coudé catheters*. **Red Robinson catheters or balloon retention catheters may each be specially constructed to have a "coudé-tip configuration." This is essentially a curved tip that allows passage of the catheter beyond certain urethral, prostatic, or bladder neck impediments that may preclude passage of a straight catheter due to impingement of the catheter tip on these lesions.**
4. *Three-way irrigation catheters*. This type of catheter has a triple lumen that has an irrigation port, a drainage port, and a port for inflating the balloon used for retention of the catheter within the bladder. Three-way irrigation catheters are particularly useful following transurethral resection of the prostate and in cases of gross hematuria to irrigate the bladder and prevent formation and retention of clots.

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5. *Technique of catheter insertion.* Insertion of a urethral catheter by the physician for either diagnostic or therapeutic reasons always involves sterile technique. Gloves should be applied and the glans and meatus of the male and the vulva and meatus of the female are then prepared with an antiseptic skin preparation solution. The catheter is then well-lubricated with sterile jelly and inserted gently into the meatus. Prior to inflation of the balloon, if a retention catheter is used, it must be certain that the tip of the catheter is within the urinary bladder and that urine is obtained. In cases in which urine does not flow freely from the end of the catheter, it is important to irrigate the catheter gently prior to inflation of the balloon to prevent inflation within the urethra. Hematuria and/or sepsis may be noted if this occurs. The catheter is then pulled gently to seat the balloon at the level of the bladder neck. It is then attached to a drainage bag with sterile technique.

## URETHRAL SOUNDS AND FILIFORMS AND FOLLOWERS

1. *General information.* These two types of instruments are often used to evaluate the urethra in cases of urethral stricture disease or for other reasons that preclude passage of a urethral catheter. They may be used in both a diagnostic and therapeutic fashion by the skilled urologist who is familiar with their use.
2. *Urethral sounds.* These metal objects come in a variety of sizes and shapes. They must be passed carefully to prevent disruption of the lower urinary tract. They are never inserted with force and must pass smoothly into the urinary bladder, where rotation of the tip of the sound is confirmed with each passage.
3. *Filiforms* and *followers.* These instruments are also useful for establishing access to the urinary bladder and dilating urethral strictures. The tiny filiform aspect of this set is used to gain access initially to the urinary bladder. Once it is established that a filiform has passed easily into the bladder, a follower may be attached and passed as a unit into the bladder. With the use of serially larger followers, it is possible to dilate the urethra.
4. *Flexible cystoscopy.* This is more commonly used than blind techniques with the above instruments. Flexible cystoscopy is used to pass a guide wire over which serially larger dilators may be passed using a modification of the Seldinger technique.

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## CYSTOURETHROSCOPY AND ASSOCIATED TECHNIQUES

1. Equipment
   a. The standard rigid cystourethroscope consists of a sheath, bridge, and lighted telescope for visualization. An irrigation port is attached to the sheath that allows gravity-directed inflow of fluid to distend the urethra and bladder and aid in visualization. The bridge essentially attaches the telescope to the sheath and may contain a variety of working ports through which urethral catheters, biopsy forceps, and alligator forceps may be passed. The lighted telescopes generally have 30- and 70-degree viewing angles that allow complete inspection within the bladder.
   b. Flexible cystoscopes, like flexible endoscopes for GI endoscopy and bronchoscopy, consist of many tiny fiberoptic bundles organized with a deflection mechanism to allow movement of the tip. The flexible scope has an advantage for male patient comfort in that it conforms to, rather than straightens, the natural curves of the lower urinary tract.
2. Technique of insertion
   a. *Males*. Insertion of the cystourethroscope into the male is best performed under direct vision following antiseptic preparation and draping. The cystourethroscope is assembled and a flow of fluid is obtained. The instrument is then introduced into the meatus and passed under direct vision through the anterior urethra. Some narrowing and voluntary constriction of the external sphincter may be noted, but this is passed with slow, gentle pressure. With the patient in the lithotomy position, it is necessary to lower the eyepiece of the rigid scope to redirect the tip of the instrument beneath the symphysis pubis, through the prostate, and into the bladder. The bladder can then be emptied and inspected with both lenses. With the flexible cystoscope, the patient can remain supine and the tip directed by manipulation of the deflecting mechanism. Flexible cystoscopy can be performed at the bedside if necessary, such as in an intensive care unit (ICU) setting.
   b. *Females*. The female patient is also placed in the lithotomy position. After proper cleansing and draping, the cystourethroscope can be inserted into the bladder either under direct vision or with the obturator in the cystoscope sheath,

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taking care to follow the course of the urethra that may be deviated due to associated pathology such as a cystocele. Once again, the bladder is inspected with both lenses and the urethra is inspected with the 30-degree lens.

3. Procedures
   a. *Inspection.* In most cases, the urethra and bladder are merely inspected under local anesthesia with these endoscopic techniques in the office setting. This allows the urologist to ascertain the presence or absence of urethral pathology, degree of anatomic obstruction, and state of the bladder mucosa and underlying musculature. It is also possible to note the presence or absence of efflux from the ureteral orifices and to judge their location and configuration. At the time of inspection of the bladder, bladder urine can be obtained for culture or cytology. The bladder can also be washed by barbotage techniques and the washings sent for cytology.
   b. *Bladder biopsies.* These may be taken under local anesthesia using cold cup biopsy forceps. Generally, however, there is some degree of associated discomfort, and, if biopsies are necessary, they are usually best performed under regional or general anesthesia to ensure an adequate specimen.
   c. *Retrograde ureteral catheterization.* The placement of small (sizes 4 to 7F) ureteral catheters may be performed without difficulty under local anesthesia. These catheters can be passed just within the ureteral orifice for retrograde injection of contrast or to the level of the kidney for relief of obstruction within the ureter, to obtain renal washings, or for the injection of contrast material for radiographic studies. They can be removed immediately or left temporarily in place.
   d. A variety of resectoscopes and specialized endoscopes are available to perform more sophisticated procedures on the urethra, bladder, prostate, ureter, and kidney.

## ULTRASOUND EVALUATION OF THE URINARY TRACT

1. *General information.* Small, portable ultrasound machines are available from a number of manufacturers. These are increasingly being used in urologists' offices and on hospital floors, in addition to radiology departments, to evaluate the urinary

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tract and to guide diagnostic procedures. Probes that have different frequencies and different configurations are designed to evaluate specific areas and aspects of the urinary tract.

2. *Renal ultrasonography.* The kidney can be evaluated for mass lesions, hydronephrosis, or the presence of stones or stone fragments.
3. *Abdominal ultrasonography.* Abdominal masses and the lower urinary tract, especially the bladder, can be imaged. Built-in computer programs allow computation of ultrasound-determined residual urine volumes. This makes a determination of bladder emptying possible without catheterization.
4. *Ultrasonography of the external genitalia.* This may be used to evaluate scrotal masses to determine whether they are cystic or solid and their relationship to the testicle and epididymis. Special Doppler probes are useful in evaluating penile blood flow in cases of erectile failure and in confirming the presence of venous reflux in suspected varicoceles.
5. *Transvaginal ultrasonography.* This may be useful in evaluating the lower urinary tract in cases of incontinence and voiding dysfunction.
6. *Transrectal ultrasonography.* This technique is most frequently used to evaluate the prostate relative to carcinoma, although it may also be used to evaluate the benign prostate with regard to size and to look for abnormalities in cases of ejaculatory dysfunction. At this time, the most common indication for transrectal ultrasonography of the prostate is for evaluation and needle localization for biopsy of the prostate. It must be emphasized that there are no specific ultrasonographic findings that definitely differentiate carcinoma of the prostate from benign lesions.

## PERCUTANEOUS SUPRAPUBIC CYSTOSTOMY

1. In instances of urinary retention when it is not possible to traverse the urethra into the bladder, various types of percutaneous suprapubic tubes may be placed with or without ultrasound guidance.
2. Equipment
   a. Percutaneous needle-guided catheters consist of a plastic drainage tube with a retention device (Malecot design or balloon) surrounding a sharpened metal trocar that is

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passed as a unit. These are typically smaller in caliber than the trocar-sheath devices described later.

   b. A peel-away sheath around a metal or plastic trocar may be passed into the bladder. After removal of the trocar, up to a 16-F catheter can be advanced into the bladder and the balloon inflated. The peel-away configuration of the sheath allows it to be removed without dislodging or damaging the catheter.

3. Technique
   a. The abdomen must be carefully examined for evidence of prior surgery or scars.
   b. The bladder must be palpable or percussible.
   c. With prior surgery or obesity, ultrasound examination of the suprapubic area should be performed.
   d. The skin is anesthetized and a small incision is made, generally in the midline, two fingerbreadths above the pubis.
   e. A spinal needle may be passed in the anticipated direction of the bladder to confirm the location of the bladder and the appropriate direction of the tract.
   f. The needle catheter device or the trocar sheath device is then passed with fairly swift but gentle pressure directly posterior into the bladder. The trocar is removed, once urine is obtained, leaving either the retention device in place or allowing passage of a separate catheter as noted previously.

## NEEDLE BIOPSY OF THE PROSTATE

1. *General information.* Needle biopsy techniques are the most accurate but not infallible means of determining whether a prostate nodule, other area of abnormality, or an elevated PSA is benign or malignant.
2. *Techniques.* The prostate can be sampled by either a transrectal or transperineal approach. To be accurate, the tip of the needle must enter the area of concern. Localization may be by digital direction but is now done almost exclusively by ultrasound guidance. Use of transrectal ultrasonography in combination with needles placed through a port in the probe has clearly improved the accuracy of this procedure and improved patient tolerance.
   a. Spring-loaded, thin-core biopsy needles are available that may be passed directly through a channel or guide in the ultrasound probe such that the tip may be seen as it enters the

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lesion of concern. These cores are obtained for sectioning. Appropriate antibiotic coverage is necessary to minimize the risk of sepsis.

b. Skinny-needle aspiration obtains cells for cytologic evaluation and is well tolerated but lacks preservation of architecture and precise accuracy of sampling.

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## Summary

The surgical subspecialty of urology deals with a well-defined organ system within the body. The urologist diagnoses and treats a wide variety of medical and surgical disorders that may have local or systemic ramifications for the patient. The history, physical examination, and urinalysis serve as the cornerstones of the initial evaluation of these patients. In addition, a variety of unique diagnostic and therapeutic instruments are available for use in the office or outpatient setting to aid in caring for those with urologic diseases. The frequency with which these problems are seen by generalists and other specialists necessitates that all practitioners have some familiarity with this field.

### CLINICAL PEARLS

1. A stone in the kidney or upper ureter may produce ipsilateral testicular pain.
2. Pain derived from the lower ureter is generally felt in the suprapubic area, bladder, penis, or urethra.
3. Although hematuria is always a danger signal, a clue to its significance may lie in whether there is associated pain or whether the bleeding is essentially painless.
4. Congenital curvature is usually in a ventral direction and, unlike Peyronie's disease, is not associated with fibrosis or formation of a plaque.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

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## Self-Assessment Questions

1. *A primary irritative process in what structure may cause pain in the ipsilateral testicle?*
2. *What is the significance of painless versus painful hematuria?*
3. *Name four causes of scrotal swelling.*
4. *What is the difference between phimosis and paraphimosis?*
5. *What is the normal role of PSA in the semen?*

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## CHAPTER 2

# Diagnostic and Interventional Uroradiology

## DIAGNOSTIC URORADIOLOGY

Parvati Ramchandani, MD

The imaging technique used to evaluate the urinary tract is dictated by the indication for which the diagnostic evaluation is being performed. Modalities currently in use include conventional abdominal plain-film radiography, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), radionuclide studies, and newer techniques such as positron emission tomography (PET). In this chapter, the role of these different imaging modalities in the management of patients will be addressed.

### Plain Films (KUB Plain Radiography)

X-ray films are rarely used in the developed world, having been entirely replaced by digital imaging in the United States and much of the west. *Computed radiograph* of the abdomen is one term used for an x-ray examination of the abdomen (KUB — kidney ureters, and bladder) performed without intravenous contrast, although it is inaccurate as a digital image is technically not a *radiograph*. Radiation exposure for an abdominal radiograph is low and is approximately 0.53 millisieverts (mSv). For comparison purposes, radiation exposure from natural background radiation is about 3 mSv per year.

#### INDICATIONS

The primary indication for a radiograph of the abdomen is to assess for the presence of radiopaque calculi, assess the results of therapy for such calculi (shockwave lithotripsy or percutaneous techniques), and evaluate urinary stents for their position and complications such as encrustation.

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As bowel content overlies the renal fossae in a patient who has not received a laxative preparation (the usual situation for a plain radiograph), small or faintly opaque stones may be hard to identify through the overlying bowel. The identification of calculi overlying the bony pelvis may also pose a challenge. Oblique images are often helpful in problem solving in such cases because the obliquity allows the kidney or ureter to be rotated off of the overlying bowel or bone and thus allow small calculi to become visible.

## Intravenous Urography

The intravenous urogram (IVU), also referred to as *excretory urogram (EU)* or *intravenous pyelogram (IVP)*, was the basic diagnostic radiologic study to evaluate the upper urinary tract for many decades. Its role in the assessment of many urologic conditions is now very limited due to the advantages offered by cross-sectional imaging modalities. IVU requires intravenous injection of radiographic contrast medium, followed by a sequence of films. Radiation exposure for an IVU (6 images) is approximately 2.5 mSv.

### INDICATIONS

1. Hematuria (macroscopic and microscopic)

   IVU provides evaluation of both the renal parenchyma and the collecting system in patents with gross or microscopic hematuria. However, CT is indisputably more sensitive for detecting renal masses compared to an IVU; although large masses are identifiable on an IVU, it is well recognized that renal masses smaller than 2 cm are often missed on an IVU (Figure 2-1). CT urography (CTU) is sensitive in detecting urothelial abnormalities and is the study most commonly used for a complete assessment of the urinary tract in patients with a history of hematuria. CT is also more sensitive than IVU in detecting urolithiasis; both small stones, and those that are faintly opaque are often not detectable on an IVU (Figure 2-2).

2. Upper urinary tract surveillance in patients with a history of a urothelial malignancy, such as bladder cancer, or positive urine cytology (Figure 2-3)

   As mentioned above, CTU has superseded IVU for this indication in clinical usage.

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3. Preoperative evaluation for select endourological procedures such as endopyelotomy

   However, CT is increasingly being used even for this indication as 3D reconstructions can be performed with high spatial resolution, allowing display of the vascular

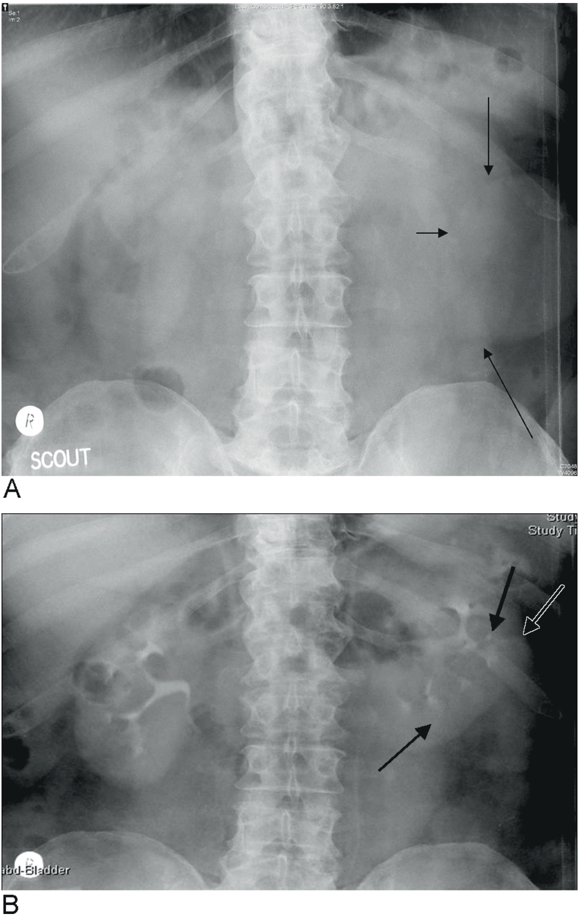

FIGURE 2-1 CT of renal cell carcinoma. **A-B,** Images from an IVU demonstrate large mass arising from the inferior aspect of the left kidney *(arrows)* on an IVU. In B, the mass is seen to cause displacement of the collecting system (arrows).

(*Continued*)

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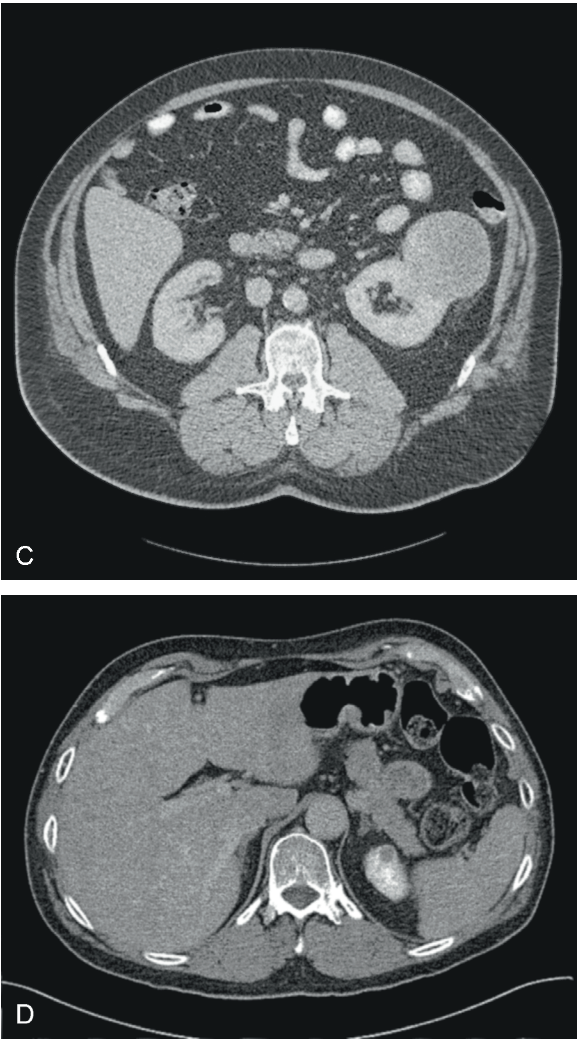

FIGURE 2-1, cont'd **C,** CT scan of the same patient demonstrates the mass well. **D,** CT scan of a different patient shows a small, left, upper-pole renal mass, which was an incidental finding on a CT done for nonspecific abdominal pain. This small lesion would not have been detected on the IVU.

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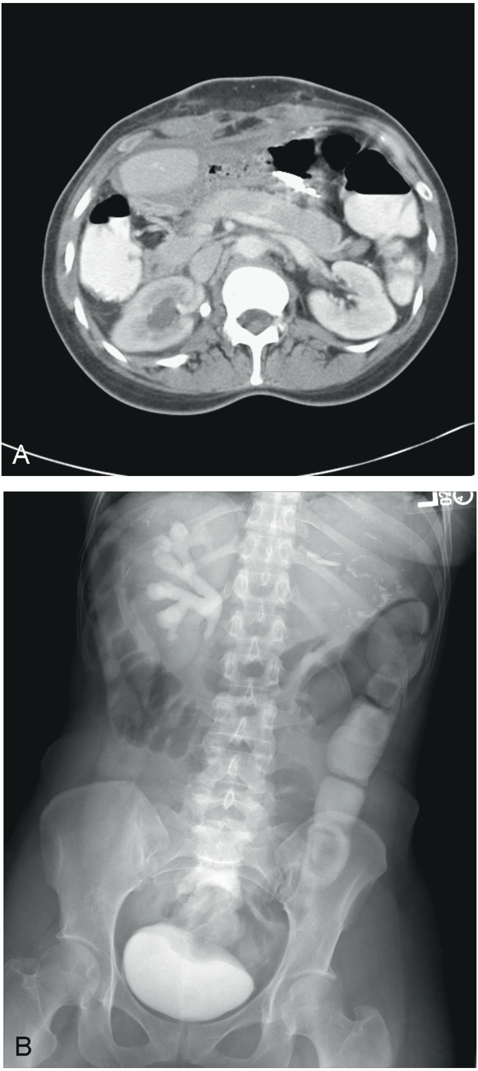

FIGURE 2-2 Acute renal colic due to a right proximal ureteral calculus. **A,** CT scan demonstrates a large calculus in the proximal right ureter. The right nephrogram is delayed indicating that the obstruction is urodynamically significant. **B,** Abdominal film obtained immediately after the CT scan shows impaired drainage of the dilated right collecting system due to the stone. Although well seen on CT, the stone was nonopaque on plain abdominal radiographs. It is important to keep in mind that even radiopaque stones will not be visible in a collecting system that is filled with contrast.

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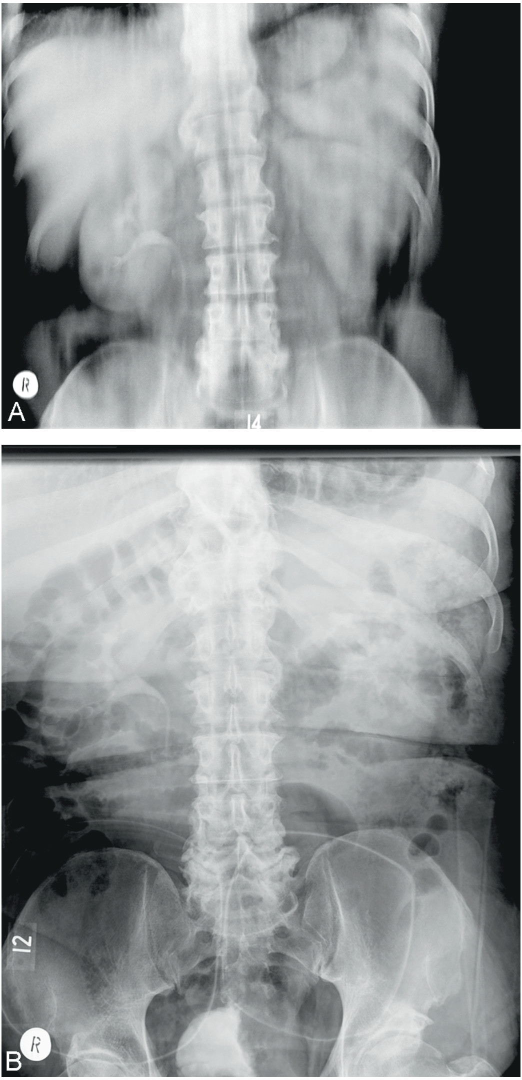

FIGURE 2-3 IVU in a patient with bladder cancer undergoing upper tract evaluation. **A,** Nephrotomogram shows delayed excretion from the left kidney due to obstructing bladder tumor. **B,** Right collecting system and ureter are normal, but the left collecting system is not opacified yet; the delay in opacification is due to the obstruction caused by the bladder tumor, which is seen as asymmetry on the left side of the bladder.

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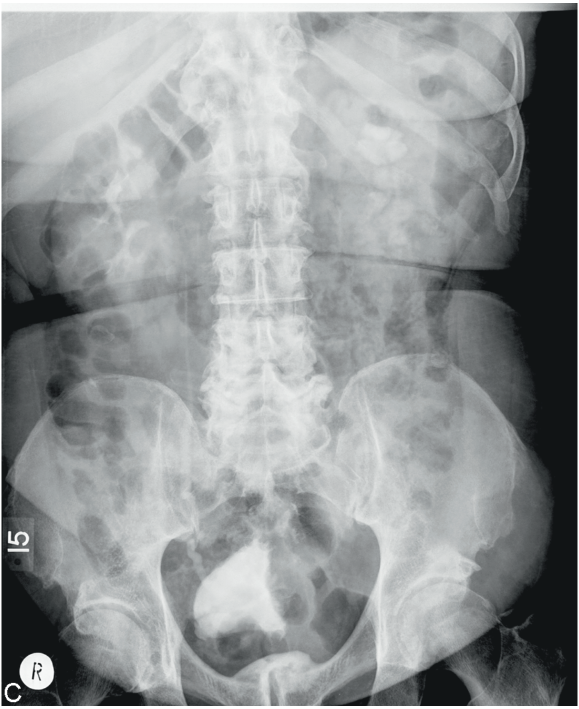

FIGURE 2-3, cont'd **C,** Fifteen minutes after contrast injection, the dilated left collecting system is just beginning to opacify. The left wall bladder tumor is clearly seen. However, it is important to note that IVU and cystography are insensitive in detection of bladder cancer.

structures and their relationship to the collecting system. Additionally, the collecting system can also be displayed in a manner similar to that seen on an IVU.

4. Postoperative evaluation following urologic procedures (Figure 2-4)

   An IVU is often performed 6-8 weeks after a urologic procedure to assess the urinary tract for complications, such as clinically unsuspected obstruction, and to have a baseline postoperative examination.

5. Complicated or unusual urinary tract infections (including tuberculosis)
6. Stone disease

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Patients who present with acute renal colic are best evaluated with noncontrast CT (no oral or intravenous contrast is necessary), which is acknowledged to be the most sensitive and specific study to exclude an obstructing ureteral calculus as the cause of the abdominal pain. This will be addressed further in the section on CT. IVUs are no longer performed in a patient with suspected renal colic because small and faintly opaque stones may not be discernible on an IVU, making it difficult to establish a conclusive diagnosis of stone-induced renal colic. Further, in patients with high-grade ureteral

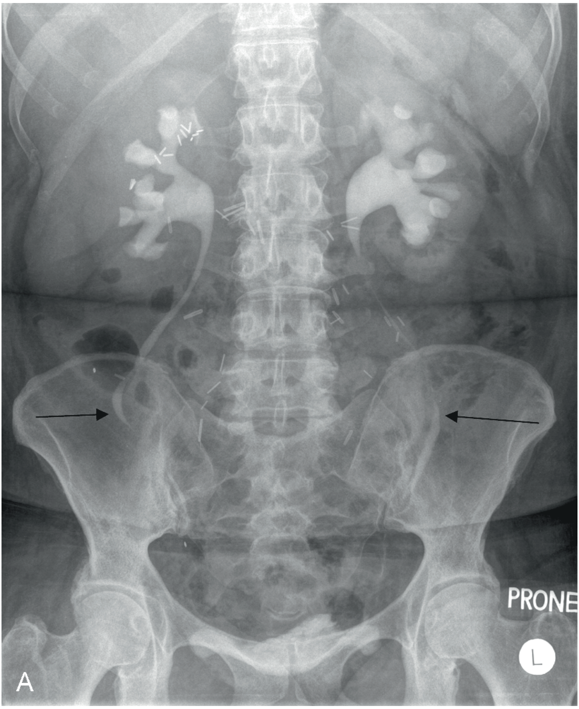

FIGURE 2-4 **A,** Follow-up IVU in a patient with retroperitoneal fibrosis who underwent ureterolysis and intraperitonealization. This prone film demonstrates residual fullness of the collecting systems, particularly on the left. The lateral bowing of the lumbar and sacral ureters is a characteristic finding after intraperitonization of the ureters.

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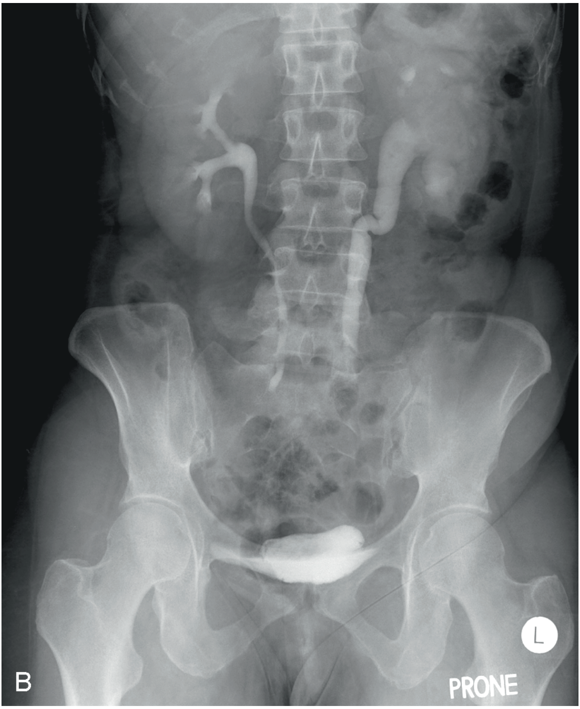

FIGURE 2-4, cont'd **B,** Preoperative IVU demonstrates hydronephrosis, more marked on the left, with normally positioned ureters.

obstruction, it can take up to 24 hours for the collecting system and ureter to opacify densely enough to determine the level of ureteral obstruction. A limited IVU (two to three films obtained after contrast administration) was advocated for pregnant women with suspected urinary colic, but a low-dose CT or MRI is a preferable study in a pregnant woman presenting with abdominal pain.

IVU continues to have a role in the management of patients with known stone disease, to help assess what would be the best therapy for an individual patient, and in follow-up after treatment, with shockwave lithotripsy (SWL), ureteroscopy, or percutaneous methods (Box 2-1).

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BOX 2-1 **Indications for Percutaneous Therapy for Stone Disease***

1. Size:
    a. Large stones (> 2-2.5 cm)
    b. Most staghorn calculi
2. Composition: Cystine calculi
3. Anatomical considerations:
    a. Compromised urine drainage (includes ureteropelvic (UPJO) obstruction, ureteral strictures, stones in dependent calices, and stones in caliceal diverticula)
    b. Abnormal body habitus (scoliosis, myelomeningocele)
    c. Congenital abnormalities such as horseshoe kidneys, fusion anomalies
    d. Postoperative states — urinary diversion, renal transplant
4. Miscellaneous indications:
    a. Certain removal of all calculous material important (airline pilots)
    b. Stones for which other treatment modalities have failed

*These clinical scenarios could also be considered to be contraindications for shock-wave lithotripsy (SWL).

## RADIOGRAPHIC IODINATED CONTRAST AGENTS

Radiographic contrast media (CM) consist of three atoms of iodine attached to a benzene ring. In the developed world, newer nonionic agents that are either of low osmolarity (LOCM — low-osmolarity contrast medium) or of iso-osmolarity, are used for intravascular administration. Contrast agents used in the past were of high osmolarity (HOCM) and are referred to as *ionic contrast agents*. Multiple studies have shown that the frequency of reactions is lower with the LOCM as compared to the HOCM when given intravenously in both the general population and in patients at higher risk for contrast reaction.

The majority of injected contrast is excreted almost entirely by glomerular filtration. A small amount may be bound to serum albumin and is then excreted by the liver and biliary system and is known as *vicarious excretion*. Patients with renal insufficiency or obstruction frequently have vicarious excretion (Figure 2-5).

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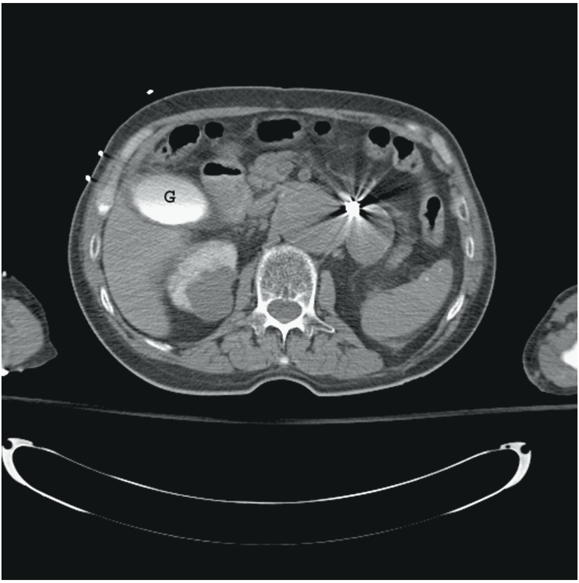

FIGURE 2-5 Contrast-induced nephrotoxicity in patient with a solitary right kidney who received multiple contrast loads for cardiac catheterization. The left kidney was removed for benign disease many years ago. Noncontrast CT scan demonstrates that the right kidney has a dense, persistent nephrogram from contrast given 48 hours previously. Note vicarious excretion of contrast into the gall bladder **(G)**. The abdominal aorta is aneurysmal.

## TECHNIQUE OF IVU

1. Patient preparation

   A thorough bowel preparation helps in optimal visualization of the urinary tract by eliminating obscuring fecal material in the bowel. Fluids are withheld overnight for better opacification of the collecting system and optimize renal concentration of the contrast medium. An empty stomach is also helpful in the event of vomiting after contrast administration, which is more common with the use of HOCM but can occur with LOCM as well.
2. A plain film of the abdomen (also known as *scout film, preliminary film, KUB film, abdominal flat plate*) is obtained.

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This is an essential component of every radiographic examination of the genitourinary (GU) tract. Urinary tract calculi can be identified only on the KUB because most urinary calculi are obscured by excreted contrast, which has the same radiographic density as calculi. Important findings such as soft-tissue masses, calcifications, and bony changes will also be disclosed on the preliminary film.

3. Contrast administration

   CM can be administered intravenously as a rapid bolus injection, slow, steady injection, or drip infusion. This is more often an individual preference rather than a matter of scientific selection. At our institution, patients receive 1 mL contrast per pound of body weight, to a maximum of 150 mL.

4. Imaging sequence (Figure 2-6)

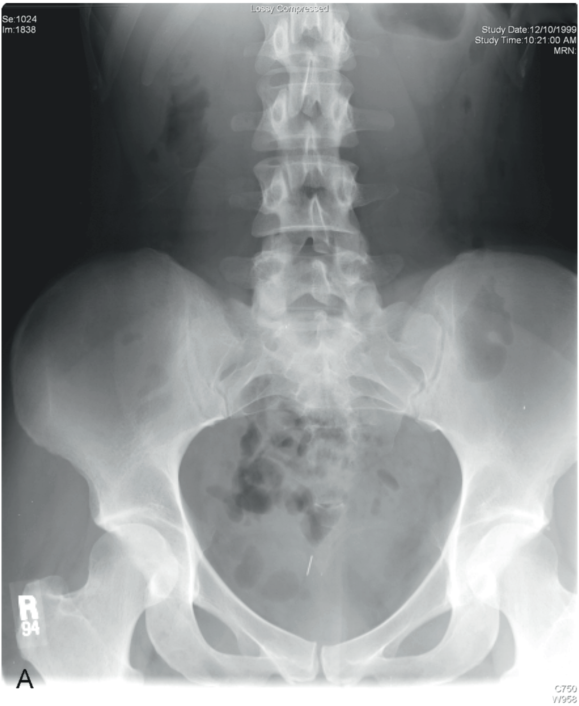

FIGURE 2-6 IVU in a young woman with microhematuria. **A,** Scout film demonstrates no abnormality.

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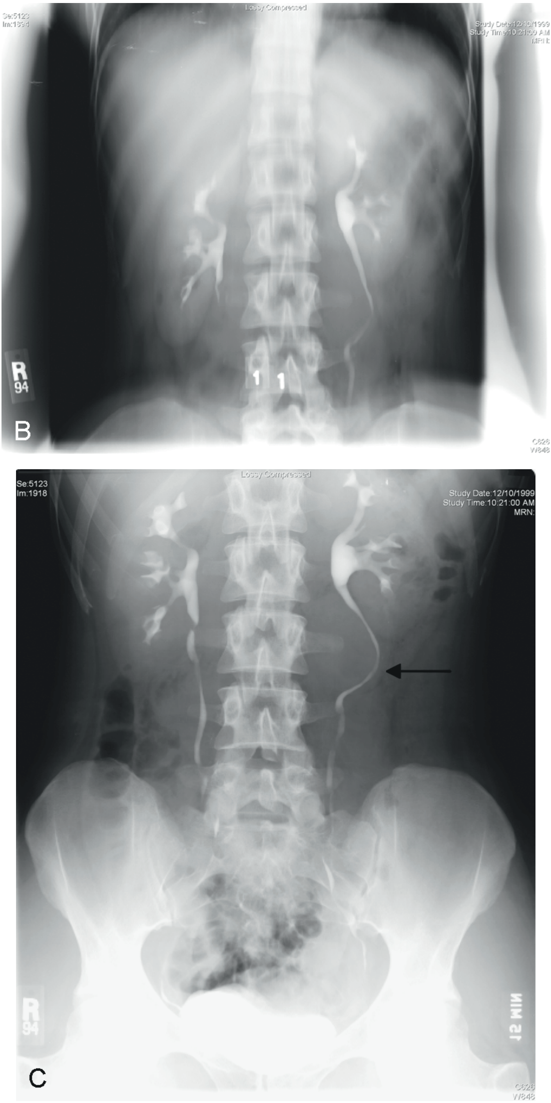

FIGURE 2-6, cont'd **B,** Selected nephrotomogram demonstrates no renal mass. Several nephrotomograms are required to demonstrate the kidneys in their entirety; not all are included here. **C,** Excretory phase demonstrates normal collecting systems but displacement of the left ureter *(arrow)*, suggesting the presence of a retroperitoneal mass.

(*Continued*)

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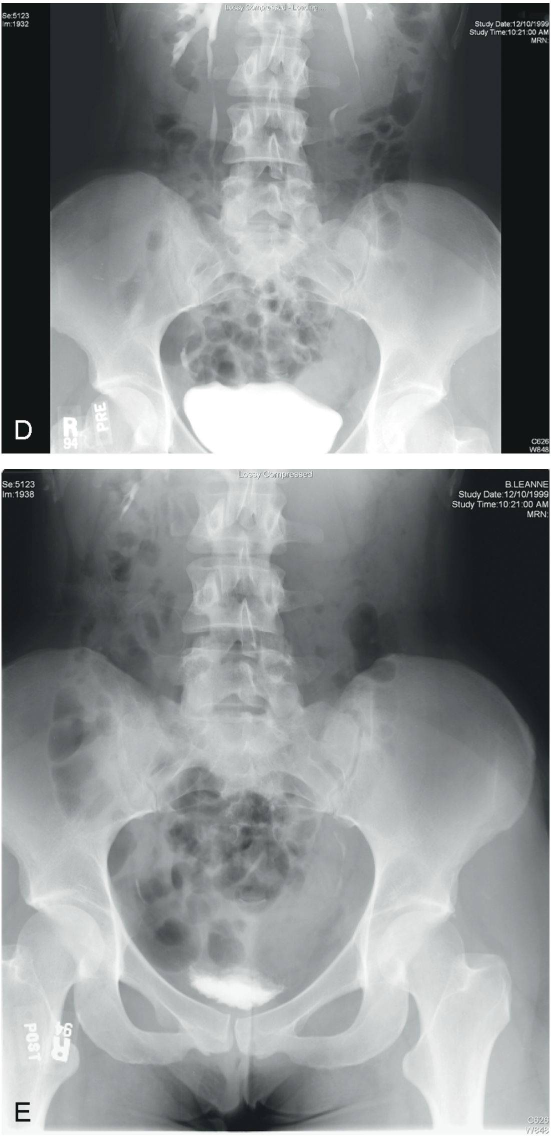

FIGURE 2-6, cont'd **D,** Prevoid film of the bladder again demonstrates left ureteral displacement but no obstruction or bladder abnormality. **E,** Postvoid film demonstrates good emptying of the bladder.

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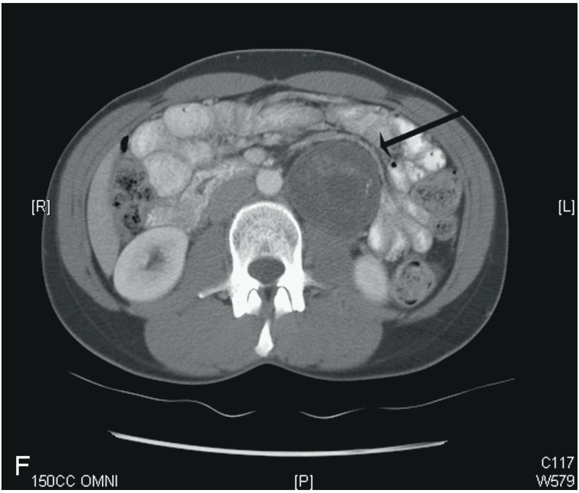

FIGURE 2-6, cont'd **F,** CT scan was recommended to evaluate the ureteral displacement and demonstrates a large retroperitoneal mass *(arrow)* which proved to be a schwannoma.

Immediately after the contrast has been injected, nephrotomograms are made to visualize the renal parenchyma (nephrographic phase) and assess for renal masses. Within 3 minutes, contrast is usually visible in the collecting systems, and several images are taken to visualize the calyces, pelves, and ureters (pyelographic phase). Images of the bladder (often including a postvoiding film) conclude the examination.

## CONTRAINDICATIONS

1. Preexisting renal insufficiency
   The administration of intravenous contrast to patients with preexisting renal insufficiency places them at risk for worsening of their renal function (contrast-induced nephrotoxicity [CIN]). Diabetic patients with renal failure due to diabetic nephropathy are more vulnerable to this complication, and if CIN occurs, it may be irreversible in these patients. Thus in patients with preexisting renal insufficiency, radiologic evaluation of the urinary tract should

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consist of renal parenchymal evaluation with US or MRI and urothelial evaluation by a combination of cystoscopy (for urinary bladder assessment) and retrograde pyelography (to evaluate the urothelium of the pyelocalyceal systems and ureters). IVU is contraindicated in patients with renal insufficiency, as are other studies requiring parenteral administration of radiographic contrast.

2. Relative contraindications
   a. Multiple consecutive contrast studies

      Patients who receive closely repeated doses of intravenous contrast are at greater risk for CIN. This risk is greater than the combined risk of two random contrast examinations. It is best to separate any two studies requiring parenteral contrast administration by at least 24 hours and preferably by 48 hours, during which time the patient should be thoroughly hydrated (see Figure 2-5)
   b. In patients with a documented allergic reaction to contrast such as urticaria (hives), cutaneous and subcutaneous edema (angioedema), upper airway (laryngeal) edema, bronchospasm, and hypotension with tachycardia, the indications for contrast administration should be carefully considered and other alternative studies performed, if possible.

      If the decision to give contrast to such patients is made, premedication with corticosteroids and antihistamines is essential, and such patients should be given LOCM, as discussed above. One example of a premedication regimen in clinical use for an elective examination is prednisone 50 mg orally, given 12, 6, and 1 hour before the examination, and diphenhydramine 50 mg 1 hour before the examination, orally or by intramuscular injection. Patients have to be cautioned about the drowsiness that accompanies diphenhydramine administration and should not undertake activities such as driving or other dangerous tasks. For emergent contrast administration, 200 mg hydrocortisone is given intravenously immediately and then every 4 hours until the examination is complete.

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c. Patients at increased risk for adverse reactions include those with a history of prior contrast reactions (four times increased risk), or a history of allergies or asthma (two to three times increased risk) as compared to patients who do not have such histories.

   Premedicating such patients prior to contrast administration is prudent. Symptoms of nausea, vomiting, or sensation of heat after contrast administration are considered to be side effects of the contrast and not allergic reactions; such symptoms are much less common with LOCM than with high osmolar contrast media (HOCM). Shellfish allergy has no particular significance for contrast administration and is managed the same way as other noncontrast allergies (e.g., allergy to bee sting, penicillin, or peanuts).

d. Multiple myeloma was long considered a risk factor for CIN with the cause believed to be precipitation of protein-contrast aggregates in the renal tubules.

   However, it is now acknowledged that myeloma does not increase the risk of CIN if the patient is well hydrated.

e. In patients with cardiac disease, contrast media administration can cause worsening of congestive heart failure due to the osmotic load.

f. Patients who are on metformin, an oral hypoglycemic agent (trade names Glucophage, Glucovance, Avandamet, and Metaglip) should discontinue the drug when they receive contrast and not resume taking their medication until their renal function is documented to be normal 48 hours after the contrast administration.

   Although metformin itself does not have an adverse effect on renal function, patients who develop renal failure on the drug (possibly due to contrast administration or other causes) can rarely develop lactic acidosis that can be fatal.

g. Delayed reactions, defined as those occurring more than 1 hour after contrast administration, can be seen with all contrast agents; they occur in 0.5% to 23% of patients and tend to be skin reactions.

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## Retrograde Pyeloureterography

### INDICATIONS

1. To investigate lesions of the renal collecting system and ureter that cannot be adequately defined by IVU or CTU
2. To visualize the collecting systems and ureters when IVU is contraindicated (renal insufficiency or severe prior contrast reaction)
3. To demonstrate the collecting systems and ureters in their entirety when IVU or CTU fail to do so
4. To visualize the ureteral stump remaining after nephrectomy in a patient with hematuria, positive urinary cytology or history of urothelial cancer.

### CONTRAINDICATIONS

1. Untreated UTI
2. Patients who cannot or should not be cystoscoped (e.g., patients recovering from recent bladder or urethral surgery)

### TECHNIQUES

1. Preliminary cystoscopy is required.
2. A ureteral orifice is identified and catheterized with a catheter, usually 5 French in size. The catheter is advanced to the renal pelvis, and contrast is instilled. The same contrast agents employed for IVU or CT are used for retrograde pyelography. To opacify the ureter alone, the ureteral orifice is occluded with a bulb occlusion catheter and contrast injected while a film is obtained.
3. Images — a preliminary image is essential to document the position of the retrograde catheters. After contrast injection, fluoroscopic images are obtained to delineate unopacified or poorly seen portions of the collecting system or ureter in question. If obstruction is suspected, an image is also obtained several minutes after removal of the ureteral catheter to evaluate the drainage of the collecting system (Figure 2-7).
4. The use of fluoroscopy is an important adjunct to Retrograde pyeloureterography (RPG). In most hospital settings, however, this requires the placement of a ureteral catheter in the cystoscopy suite and the subsequent transport of the patient to the radiology department for catheter injection.

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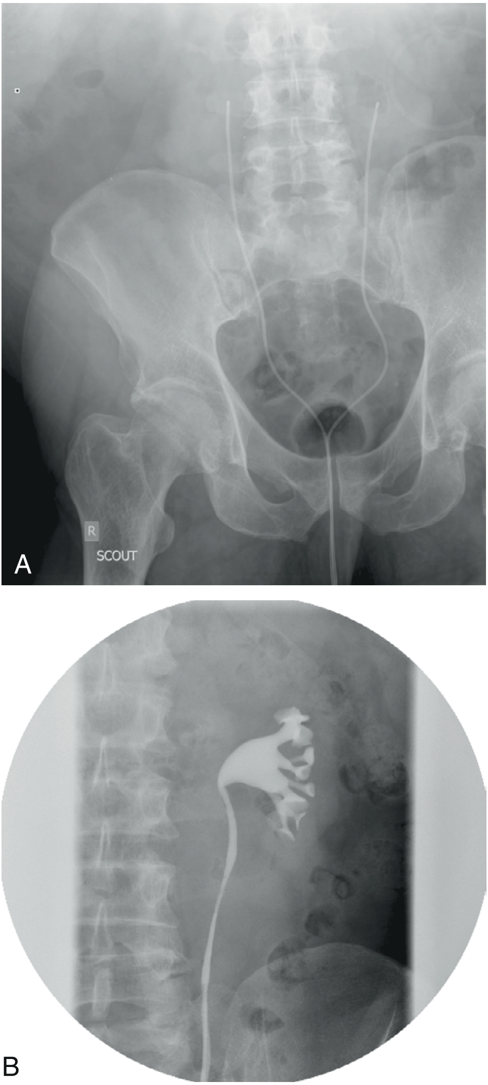

FIGURE 2-7 Retrograde pyelogram and the preliminary scout image. **A,** Bilateral catheters with tips in lumbar ureter at L3 level. Contrast injection through the left catheter. **B,** Normal left collecting system and ureter. Note the excellent depiction of the urothelium.

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5. RPG may be impossible in some patients, such as those with very larger prostates, in whom the gland overlies the ureteral orifices, preventing proper catheter placement. At times, even though the orifice is identifiable, it may not be possible to catheterize it, such as may occur with tortuous ureters or after ureteral reimplantation in a native system or a renal transplant.
6. Radiation exposure with all fluoroscopic procedures varies with the equipment, size, and body habitus of patient, fluoroscopy times, and factors such as collimation and distance between x-ray source and the patient.

### COMPLICATIONS

1. Perforation of the ureter is uncommon. When it does occur, there is usually no serious sequela. Contrast extravasation outside the collecting system does not usually result in any harm. In some cases of perforation associated with a large amount of urine leakage, diversion of urine with a ureteral stent may be required for a few weeks.
2. A too vigorous injection of contrast material in an infected urinary tract may disseminate bacteria into the bloodstream and kidney, causing bacteremia and rarely pyelonephritis. This risk increases in the presence of a urinary tract obstruction. Fortunately, the normal antegrade flow of urine is usually enough to wash out any bacteria that may have been introduced during the procedure. Patients usually receive prophylactic periprocedural antibiotics as well.
3. Absorption of contrast agent can occur if there is perforation of the collecting system or pyelosinus extravasation due to overdistention. In patients truly allergic to contrast media, the retrograde approach does not obviate a systemic contrast reaction, although reactions are much less common than after IV injection. Patients with a history of contrast allergy should receive premedication with corticosteroids and antihistamines.

## Antegrade Pyelography

### INDICATIONS

1. To visualize the urothelium of the upper urinary tract when an IVU is unsatisfactory and RPG cannot be done

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2. In patients with a history of urothelial malignancy and high-grade obstruction of a collecting system, an antegrade pyelogram may be the only way to evaluate the urothelium of the collecting system and ureter. Contrast excretion in an obstructed system is impaired, and thus intravenous contrast administration for either an IVU or CTU will not depict the collecting system well enough to exclude upper urinary-tract urothelial lesions.
3. In patients with renal transplants who have azotemia in association with a dilated collecting system, antegrade pyelogram can help determine whether the transplant collecting system is obstructed or not. The ureteroneocystostomy created to drain a renal transplant is often difficult to cannulate cystoscopically.

## CONTRAINDICATIONS

Bleeding diathesis

## TECHNIQUES

The renal pelvis is percutaneously punctured with a 20- or 21-gauge thin-walled needle from a posterior or posterolateral approach. Localization is provided by means of contrast excreted after an IV injection or with ultrasound in a dilated collecting system. Contrast is injected, and images are exposed under fluoroscopic control.

## COMPLICATIONS

These are similar to a percutaneous nephrostomy (PCN).

1. Inadvertent puncture of neighboring structures may occur. Although puncture of the renal vein, kidney, parenchyma, or liver and spleen is possible, few if any complications result because of the small size of the needle.
2. Some extravasation usually occurs with many antegrade pyelograms. However, the puncture site is very small and seals rapidly after the needle is removed.
3. Entry into the nondilated collecting system may be difficult and time consuming and, on rare occasions, may fail completely.

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## Cystography

### INDICATIONS

1. Suspected bladder trauma

   Bladder opacification by contrast excreted during an intravenous injection for an IVU or CT is unreliable in assessment for bladder ruptures. The bladder should be opacified by means of a catheter placed in the bladder until a detrusor contraction is elicited to reliably exclude a bladder rupture. The study should not be terminated at a predetermined volume of contrast because a detrusor contraction may occur at variable intravesical volumes in different individuals, and the bladder should be filled until a detrusor contraction occurs.
2. Evaluation of fistulae involving the urinary bladder (Figure 2-8)
3. Evaluation of healing following bladder or distal ureteral surgery

### CONTRAINDICATIONS

There are no contraindications to cystography itself. When a patient has sustained significant pelvic trauma, the integrity of the urethra must first be established before passing a ureteral catheter. This may often require that retrograde urethrography precede cystography.

### TECHNIQUE

1. After a preliminary image, a urethral catheter is passed, and CM is instilled into the bladder. Images of the filled bladder are made in multiple projections. The bladder is then allowed to empty through the catheter, after which a drainage image is obtained. The postdrainage image is extremely important because small leaks from the posterior wall may be obscured by a contrast-filled bladder and be visible only after the bladder has been drained of contrast.
2. Cystography may also be performed through an existing cystostomy tube or via suprapubic puncture.

### COMPLICATIONS

Complications of cystography are rare. Excessively forceful injection may result in disruption of a fresh suture line.

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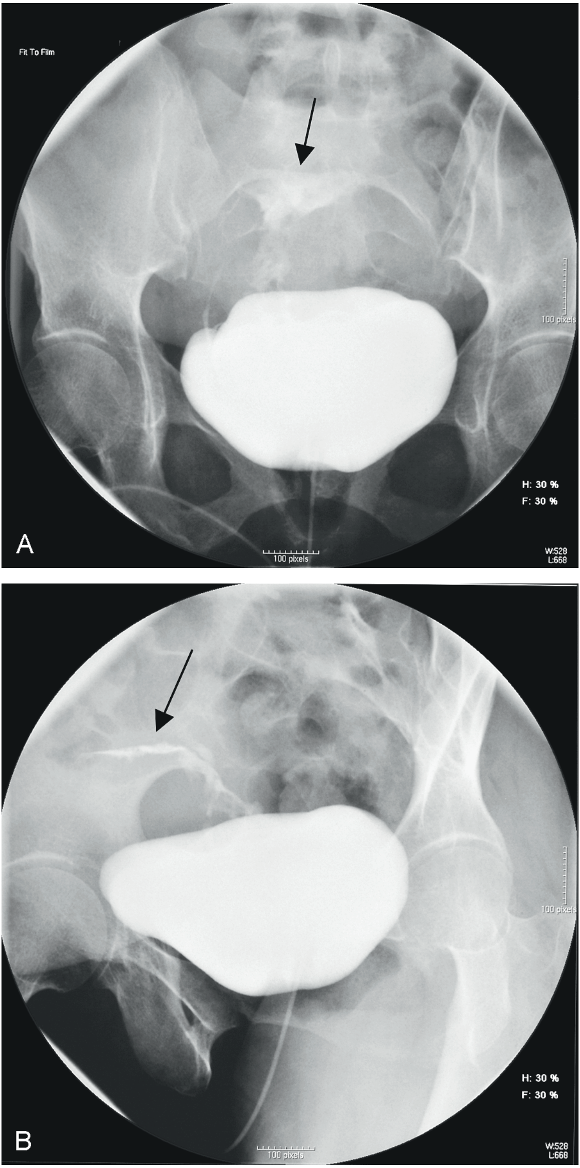

FIGURE 2-8 **A-B,** Frontal and oblique views of cystogram in a woman with vaginal leakage a few weeks after cesarean section delivery. Opacification of the uterus *(arrow)* from the urinary bladder is seen.

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## Modifications of Cystography

### CT CYSTOGRAM

Since most patients with significant abdominal or pelvic trauma undergo a CT scan for evaluation, the addition of a CT cystogram to assess the bladder is helpful in patients with significant pelvic injury. After the initial set of CT images have been obtained, diluted contrast is injected through an indwelling Foley catheter, and scanning is repeated through the pelvis. Most published reports indicate that CT cystograms and conventional cystograms have comparable sensitivity in detecting bladder injury. An advantage of CT is that the patient does not have to be turned into different projections (an obvious advantage in patients with pelvic fractures) for optimal evaluation, and a postdrain image is unnecessary because the entire bladder is well seen on a CT.

When evaluating a patient for a suspected fistula involving the bladder, a CT cystogram helps in demonstrating the fistula well. CT is the most sensitive imaging technique in patients with suspected colovesical fistulae due to complications of diverticulitis.

## Voiding Cystourethrogram

Voiding Cystourethrogram (VCUG) demonstrates the anatomy of the lower urinary tract during micturition and allows assessment for vesicoureteral reflux.

### INDICATIONS

1. Recurrent urinary tract infections, especially in children, in whom reflux is not uncommon
2. Evaluation of the posterior urethra in the male and the entire urethra in the female

   VCUG is used to evaluate urethral stricture disease, posterior urethral valves in the infant male, and the postoperative urethra (Figure 2-9). In the female, it is a primary method of evaluating for suspected urethral diverticula.
3. Evaluation of certain voiding dysfunctions (e.g., detrusor-external sphincter dyssynergia, neurogenic bladder)

   VCUG can be combined with simultaneous pressure-flow recordings for a study known as *videourodynamics*.

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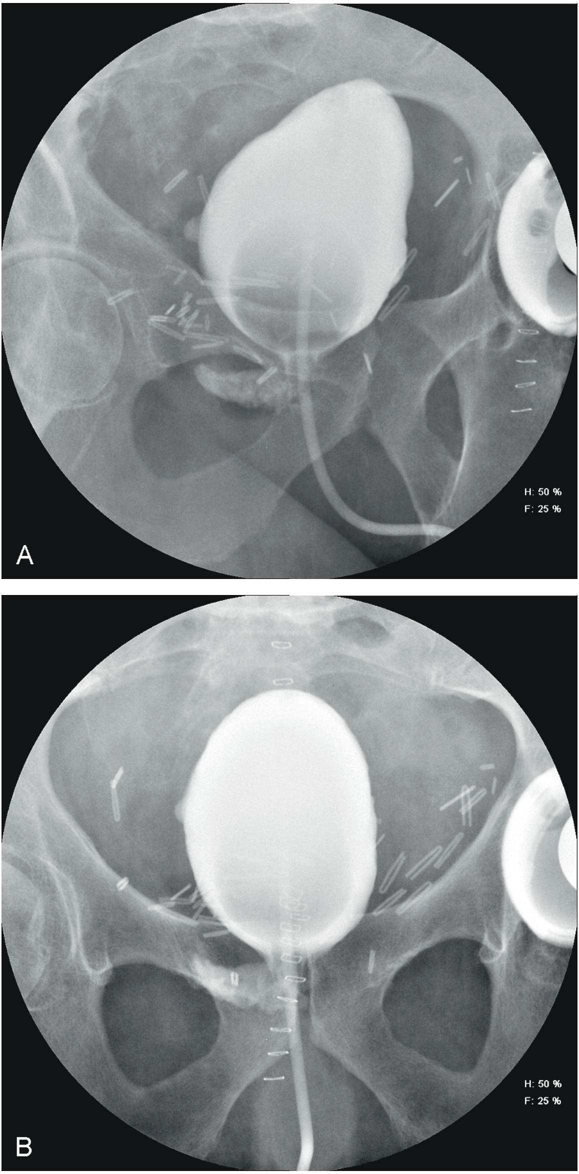

FIGURE 2-9 VCUG 10 days after radical retropubic prostatectomy demonstrates leak from the right posterior aspect of the anastomosis. Study done a week later shows healing of the leak. **A,** Left posterior oblique view. **B,** Frontal view.

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4. For the evaluation of an ectopic ureter thought to insert into the urethra

   Reflux into such ectopic ureters is fairly common.

### CONTRAINDICATIONS

Acute urinary tract infection

### TECHNIQUES

1. This procedure is best performed under fluoroscopic control.
2. The bladder is catheterized and filled with water-soluble CM. HOCM is usually used for this study because a large amount of contrast is required (300 to 600 cc), and adverse reactions with contrast injection into the bladder are uncommon. When the patient has a strong desire to void, the catheter is withdrawn and the patient voids. Fluoroscopic images are obtained during voiding, and an estimate of the completeness of bladder emptying is made. In patients who have undergone recent bladder-neck or urethral surgery, voiding around an indwelling urethral catheter is initially performed to look for contrast extravasation. If none is seen fluoroscopically, the urethral catheter may be removed and another void documented fluoroscopically.
3. Although the bladder is filled with the patient recumbent, voiding is usually performed with the patient standing.

### COMPLICATIONS

These are the same as those listed under cystography.

## Retrograde urethrogram

### PURPOSE

Retrograde urethrogram (RUG) provides detailed visualization of the anterior urethra in the male. The procedure has little or no application in the female. On a RUG, the posterior urethra is incompletely visualized because the closed external urethral sphincter resists the retrograde flow of contrast into the posterior urethra. Complete evaluation of the anterior and posterior urethra in a male requires both a VCUG and a RUG (Figure 2-10). Although the anterior urethra is seen on a VCUG, a diseased anterior urethra is better demonstrated on a RUG.

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## INDICATIONS

1. Detailed delineation of suspected or known urethral stricture (most common indication)

   The study is also useful to assess the results of surgery for urethral stricture repair.
2. Suspected urethral trauma

   RUG should be routinely performed before attempting passage of a urethral catheter in a male patient with a pelvic fracture.
3. Demonstration of urethral diverticula, fistulae, and neoplasms

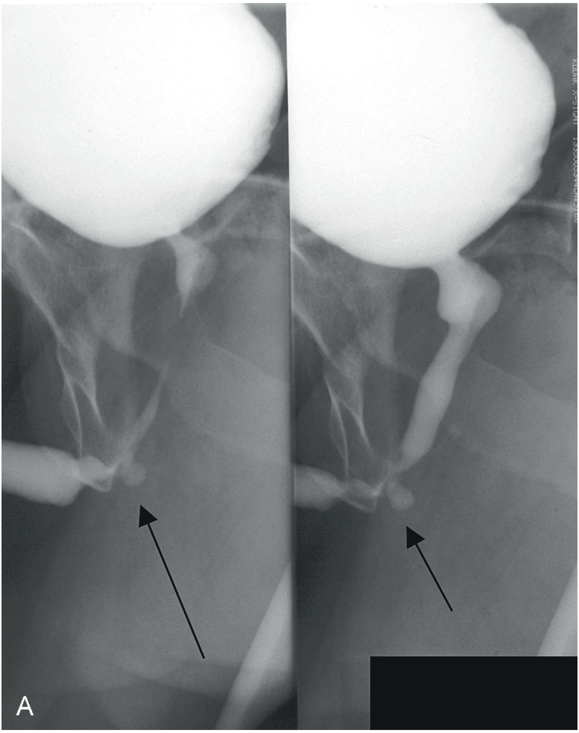

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FIGURE 2-10 Straddle injury. **A,** VCUG through a suprapubic catheter demonstrates irregularity of the bulbar urethra at injury site *(arrows).*

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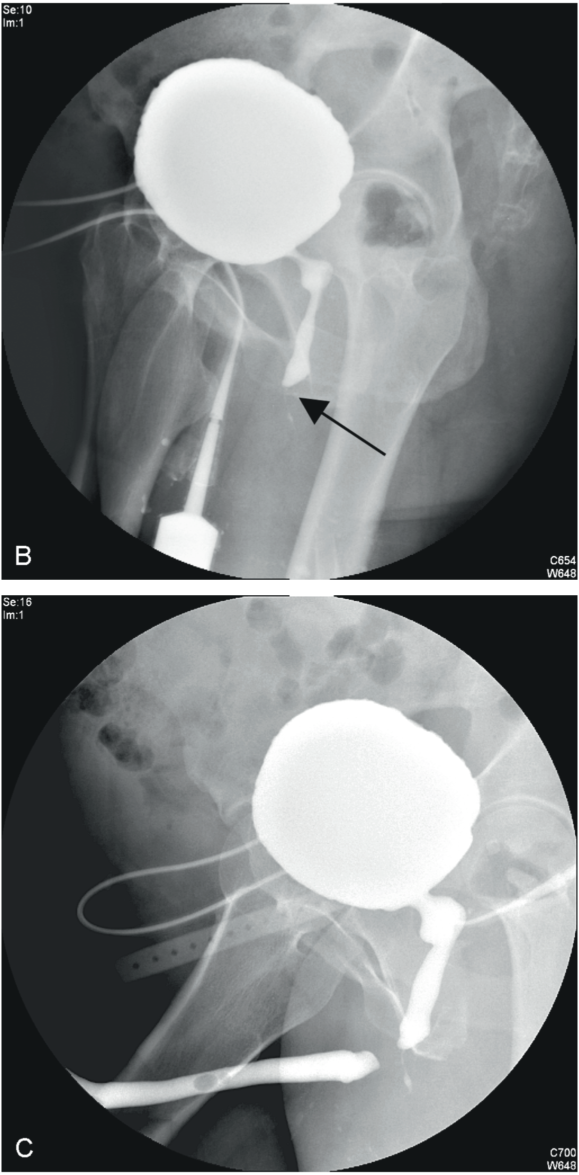

FIGURE 2-10, cont'd **B,** VCUG demonstrates urethral occlusion at injury site *(arrow)* 5 weeks later. **C,** Combined VCUG and RUG help in assessing the length of occlusion more optimally.

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### CONTRAINDICATIONS

1. Acute urethritis, as discussed below.
2. Patients who are allergic to contrast should be pretreated. LOCM should be employed in this situation.

### TECHNIQUE

1. A Foley catheter is placed with sterile technique, and the Foley balloon is inflated in the fossa navicularis. Approximately 2 mL of contrast is sufficient to seat the balloon in a stable fashion in the urethra. It is preferable to use contrast to fill the balloon because air is more compressible than fluid, and an air-filled balloon can extrude during the study.
2. LOCM is then injected, and fluoroscopic images of the fully distended urethra are taken.

### COMPLICATIONS

Reflux or intravasation of contrast from the urethra into the surrounding corpus spongiosum can occur during RUG. Such reflux is usually minimal and without clinical consequence except in the presence of urethritis when bacteria may be forced into the bloodstream. In patients with venereal warts, the procedure should not be performed until the active infection has been controlled, in order to avoid spreading the infection to the urethra. Spongiosal intravasation is more apt to occur in patients with high-grade urethral strictures.

## Loopogram and Pouchogram

Anastomosis of the ureters to an isolated intact segment of ileum or transverse colon (loop) or to a detubularized large or small bowel segment (pouch) is the most common method of establishing permanent urinary diversion (Figure 2-11). The isolated bowel loop serves as a conduit to propel urine outward toward the stoma, and a urine collection bag is applied to the stoma to collect the urine. A detubularized pouch functions as a continent reservoir rather than a conduit. Pouches can be connected to a cutaneous stoma or be anastomosed to the urethra (orthotopic diversion). Cutaneous continent pouches require intermittent catheterization for emptying, whereas patients with orthotopic

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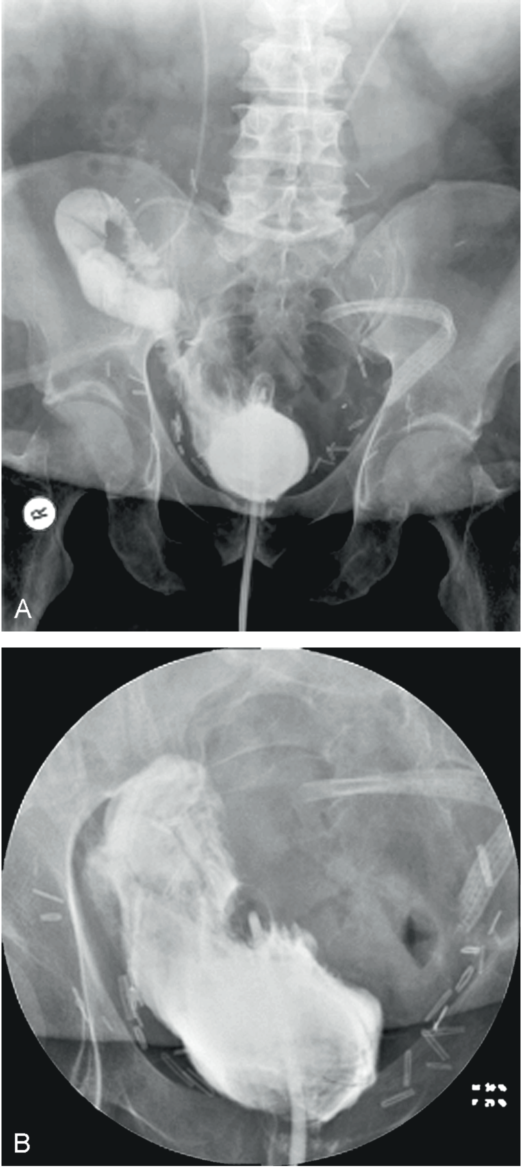

FIGURE 2-11 Normal examination of a Studer pouch 3 weeks after surgery. **A,** An image taken early in the filling process. **B,** An image after the pouch is filled. Note that early filling image better demonstrates the afferent limb than the image taken when the pouch is fully distended.

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pouches void by increasing abdominal pressure to empty the pouch. Radiologic examination of urinary diversions is referred to as *loopography* or *pouchography*.

## INDICATIONS

1. To evaluate the bowel conduit or reservoir for suspected intrinsic disease (e.g., filling defect, anastomotic or other leaks, loop stenosis), capacity, or peristaltic activity
2. To visualize the upper urinary tract by reflux

   Reflux is normal with ileal conduits but unpredictable in continent diversions. If a patient with a continent diversion requires urothelial evaluation beyond that provided by an IVU or CTU, antegrade pyelogram is usually the next step.
3. To evaluate patients with loop diversion whose upper urinary tracts show deterioration on serial IVUs or ultrasonogram (i.e., worsening hydronephrosis, renal calculi, or renal scarring) or whose renal function is diminishing

   In such patients, the absence of reflux from the ileal loop into the ureters may indicate ureteroileal obstruction.

## CONTRAINDICATIONS

There are no contraindications to the retrograde study of a urinary conduit or reservoir other than active urinary tract infection. Because the urinary tract of patients with urinary diversions is usually colonized with bacteria, prophylactic antibiotics are administered prior to the procedure to prevent bacteremia after the procedure.

## TECHNIQUE

1. A preliminary image is obtained. The stoma of an ileal conduit is catheterized with a 14 or 16 French Foley catheter with aseptic technique. The balloon is inflated just below the anterior abdominal wall, and the conduit is filled with LOCM until the ileum is well distended. Fluoroscopic images are obtained with particular attention given to the presence or absence of reflux. Images of the collecting systems and ureters are obtained to evaluate for urothelial abnormalities. The catheter is then removed and the conduit and upper urinary tracts evaluated for emptying.

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2. A continent urinary pouch or reservoir is also evaluated fluoroscopically. The stoma (for a cutaneous diversion) or urethra (for an orthotopic diversion) is catheterized and a Foley catheter placed into the reservoir. The reservoir is opacified with CM to capacity, which varies with time. At maturity, it should accommodate several hundred mL of fluid. Filling defects and leaks are documented if present. Nonopaque mucus in the reservoir is an expected finding.

   Although many pouches do not normally allow for ureteral reflux, reflux may be observed with a Studer pouch in which the ureters are anastomosed to an isoperistaltic afferent loop of ileum, which drains into a detubularized ileal pouch (see Figure 2-11). Although reflux does not occur in a normally functioning Studer pouch, the elevated intraluminal pressures generated during retrograde pouch opacification may fill the isoperistaltic afferent limb and diverted ureters.

### COMPLICATIONS

Pyelonephritis may accompany forceful reflux of infected urine.

## Angiography

Angiography refers to the radiologic study of both the arterial and venous systems. Studies pertinent to the study of the urinary tract include:

1. Arterial: aortography, renal arteriography, and adrenal arteriography
2. Venous: inferior venacavography, renal phlebography, adrenal phlebography, and gonadal phlebography

### INDICATIONS FOR RENAL ARTERIOGRAPHY

1. To evaluate for suspected renal artery stenosis (RAS)

   RAS is a cause of potentially reversible hypertension and renal insufficiency, particularly in elderly patients. Many screening tests have been used in an effort to noninvasively diagnose RAS. CT angiography and MR angiography are the most frequently used imaging techniques; the latter is preferred in patients with renal insufficiency to reduce the risks of contrast-induced nephrotoxicity, which is

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more frequent with iodinated contrast materials than with gadolinium-based contrast agents used for MR. In patients with severe chronic kidney disease, gadolinium-based contrast agents have been associated with the development of a debilitating condition called *nephrogenic systemic fibrosis* and are contraindicated. Patients with significant truncal stenosis of the renal artery and fibromuscular dysplasia are treated with angioplasty. Lesions at the renal artery ostia are resistant to angioplasty and require primary stenting. Randomized trials that compared renal artery angioplasty with best medical therapy do not indicate that angioplasty is a convincingly superior treatment.

2. Neoplasms

   Since the development of CT and MRI, angiography is almost never used in the diagnosis of renal masses. It is still used occasionally for the preoperative embolization of large, hypervascular renal cell carcinomas and for prophylactic embolization of angiomyolipomas that are larger than 4 cm in size, to prevent spontaneous hemorrhage.
3. Renal trauma

   Most traumatic parenchymal and vascular lesions can be satisfactorily imaged by CT. Angiography is usually reserved to demonstrate an arterial bleeder or arteriovenous communication prior to embolization.
4. For the evaluation (and potential ablation) of vascular abnormalities such as aneurysms and arteriovenous malformations suspected on other imaging studies
5. CT angiography or MR angiography are preferred to catheter angiography to provide a preoperative arterial “road map” for surgery when there is a high risk of anomalous vascular supply such as in a horseshoe kidney or an ectopic kidney.

   Also, in the preoperative evaluation of potential renal donors, CT angiography and MR angiography have supplanted catheter angiography in most institutions.

## INDICATIONS FOR ADRENAL GLAND ANGIOGRAPHY

1. Ablation of adrenal function by embolization
2. For adrenal vein sampling to diagnose functioning adrenal tumors.

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### INDICATIONS FOR GONADAL PHLEBOGRAPHY

1. Gonadal phlebography is valuable in evaluating varicoceles and in treating them by means of venous occlusion with balloons, coils, or sclerosing agents.
2. High-resolution CT and MRI are preferred to gonadal phlebography to search for a nonpalpable undescended testis.

## Radionuclide Imaging

Radionuclide imaging is used to assess renal vascular perfusion, renal function, and obstruction.

### INDICATIONS

1. Assessment of renal function

   Following a bolus injection of radionuclide, computer analysis of radioactivity plotted against time allows analysis of blood clearance rates to determine the glomerular filtration rate and effective renal function. Ascertaining the relative function of the kidneys is especially important when decisions regarding nephrectomy versus salvage operation must be made in patients with renal malignancies. In cases of severe hydronephrosis, split renal functions before and after a period of nephrostomy drainage allows assessment of residual renal functional in the previously obstructed kidney.
2. Hypertension

   Differential renal blood flow studies (performed before and after the administration of an angiotensin-converting enzyme inhibitor (ACEI) such as captopril) detect approximately 85 percent of cases of renal vascular disease. Difficulties with isotope screening in hypertension include problems in distinguishing unilateral renovascular lesions from unilateral renal parenchymal disease and problems recognizing bilateral vascular stenoses. The accuracy of the examination is decreased in patients with renal insufficiency, bilateral renal artery stenoses, and with chronic use of ACEIs.
3. Evaluation of renal transplant failure

   Isotopic methods of imaging the kidney are very helpful in evaluating renal transplant complications, including obstruction, extravasation, and stenosis of the arterial anastomosis. Differentiation between acute tubular necrosis and transplant rejection is a more difficult task.

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4. Questionable or intermittent obstruction

   The presence of intermittent obstruction, especially at the ureteropelvic junction (UPJ), is often difficult to evaluate and confirm. Using radionuclide methods, the rate of emptying of the collecting system after a diuretic challenge (washout or Lasix renogram) can be evaluated and compared to standard emptying profiles. A normal kidney puts out over 76% of the activity that enters it within 20 minutes.
5. Evaluate for urine leak.

   Small urinary leaks in patients who cannot receive iodinated contrast can be detected readily with radionuclide studies. Renal transplant patients with impaired renal function and suspected urinary leak are the classic case where radionuclide studies are very helpful in evaluating for urinary leak.
6. Evaluate for vesicoureteral reflux.

   VCUG is used for initial evaluation of suspected reflux in children, so that the anatomy of the lower urinary tract can also be assessed, a task not possible with radionuclide imaging. However, radionuclide cystogram is the follow-up procedure of choice for proven reflux because it is more sensitive than VCUG and imposes less of a radiation burden on the patient. Using agents such as $^{99m}$Tc-DMSA, the renal scarring, which is often the consequence of reflux, can also be demonstrated.
7. The "acute" scrotum

   When testicular torsion is suspected, an ultrasound examination with Doppler is the initial study. Radionuclide flow study of the scrotum will demonstrate the viability of the testis and compare its perfusion to the opposite side. Increased nuclide perfusion favors epididymitis over torsion.
8. Adrenal gland

   $^{131}$Iodine metaiodobenzylguanidine (MIBG), an adrenal medullary imaging agent, can readily and easily localize pheochromocytomas. Cholesterol analogues (lodine-131 NP-59) have also been synthesized and have proved helpful in localizing hyperfunctioning and hypofunctioning adrenal lesions.
9. PET scanning

   In urogenital imaging, the most widely used tracer is F$^{18}$-fluorodeoxyglucose (FDG), which is taken into cells through glucose transporters. Many tumors have increased glucose uptake, and therefore concentrate FDG. FDG is normally excreted by the kidneys through urine, which limits its utility

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in evaluating the kidneys. Modern machines have a CT scanner incorporated into the PET machine, allowing accurate localization of sites of increased uptake.

FDG-PET scanning is used in restaging testicular cancer after chemotherapy because it appears to be more accurate than CT for detecting recurrence. To date, FDG-PET has not shown much value in the evaluation of prostate or bladder cancer.

### CONTRAINDICATIONS

Radionuclides should not be administered during pregnancy. There are no other contraindications to the use of radionuclide studies for diagnostic purposes.

### TECHNIQUE

Techniques vary depending on the information desired. In general, a tracer dose of radioactive isotope bound to a specific pharmaceutical agent is administered and the patient is placed beneath a gamma camera where images (scans, scintigrams) are generated at intervals depending on the information sought. For flow studies, images are taken as frequently as every few seconds. For anatomic information, images are obtained by accumulating counts for several minutes. These images may be taken sequentially for as long as several hours, and under certain circumstances may even be delayed up to 24 or 48 hours. Recently, techniques for obtaining tomographic scintigraphy (single-photon emission computed tomography [SPECT]) have considerably improved the anatomic information provided by radionuclide images. When evaluating renal function, small radiation detectors or gamma cameras placed directly over the kidneys can be used to generate time-radioactivity curves. This is known as a *renogram*.

### COMPLICATIONS

There are no complications of nuclear medicine diagnostic procedures. The radiation doses involved are modest and often less than those for comparable conventional radiographic studies or CT.

## Ultrasonography

Ultrasound (US) can be used to image most parts of the GU system. It is a noninvasive study with no radiation exposure. Administration of contrast is not required, although newly developed US contrast

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agents often enhance the diagnostic yield of the examination. Characteristics of blood flow can be determined by US. The resolution of US imaging is limited in large and obese patients.

## TECHNIQUES

Two types of sonographic imaging are commonly used in the urinary tract: Real-time gray-scale imaging is used to depict the architecture and anatomy of the organ. Real-time imaging allows consistent modification of transducer position to obtain optimal projections. Doppler or flow imaging is used to assess the vascularity of the organ and masses and is usually combined with real-time gray-scale imaging.

Newer advances in US include advances in image presentation such as 3D imaging and extended field-of-view imaging, so that data can be presented in a single image to facilitate the depiction of spatial relationships.

## COMPLICATIONS

None is known.

## INDICATIONS

### Kidney

1. Evaluation of a renal mass

   US can detect fluid-filled renal masses with more than 98% accuracy. Solid-mass lesions larger than 1 cm in diameter are also routinely identified, especially if they are in the renal cortex. The US appearance of cysts and solid masses is quite distinctive, although complex or complicated cysts may share certain imaging characteristics of solid lesions. The detection of neoplasms is aided by demonstrating flow within them by means of color-flow or power Doppler. US may also demonstrate intravenous and intracaval tumor extension in renal neoplasms. The ability to identify, characterize, and stage a renal mass is dependent on the depth of the lesion beneath the skin and the body habitus of the patient.
2. Impaired renal function

   In patients with renal insufficiency, US is helpful in assessing the size of the kidney and excluding urinary obstruction as a cause of the renal failure. Dilated renal pelves and calyces usually indicate obstructive uropathy (Figure 2-12). Alteration

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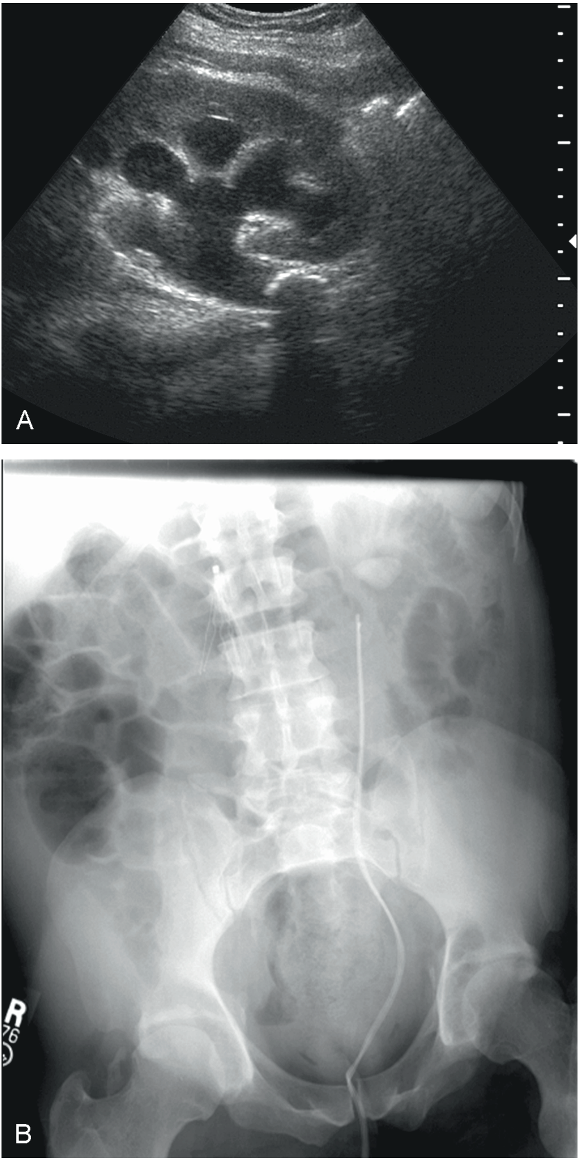

FIGURE 2-12 Hydronephrosis due to a proximal ureteral stone. **A,** Renal ultrasound (US) shows marked hydronephrosis proximal to a shadowing echogenic calculus. **B,** Retrograde catheter was distal to stone and did not drain left kidney.

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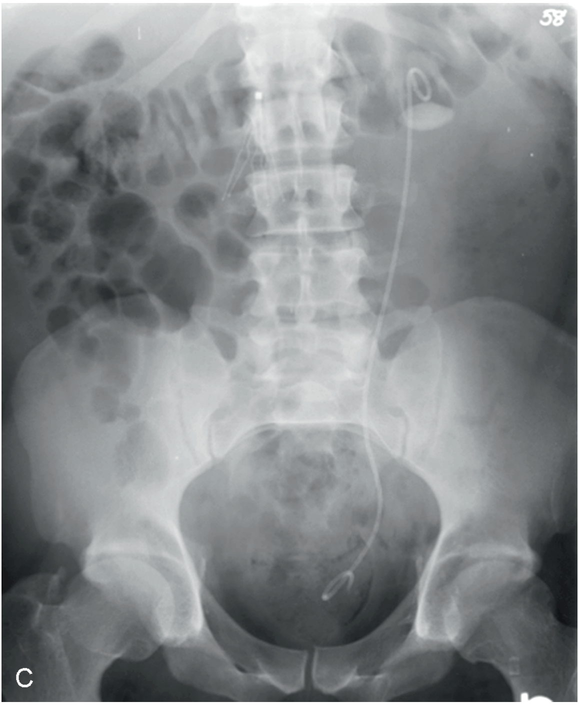

FIGURE 2-12, cont'd **C,** Double-pigtail internalized stent was placed, and patient underwent shockwave lithotripsy (SWL).

in the normal echogenicity of the kidneys is seen in patients with medical renal disease. The kidneys may be smaller and more echogenic than normal.

3. As a guide to biopsy and other interventional procedures

    By visualizing the kidney directly, entry into the kidney is facilitated for percutaneous renal biopsy or for entry into dilated renal collecting systems for antegrade pyelography preparatory to percutaneous nephrostomy. A needle guide mounted on the US transducer facilitates the procedure.

4. Evaluate filling defects seen in the collecting system on IVU or RPG

    These are most commonly caused by nonopaque calculi, urothelial neoplasms, and blood clots. Renal calculi are markedly echogenic, produce acoustic shadowing, and are readily

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detectable by US (see Figure 2-12). Clots and tumors may also be demonstrated, but not necessarily easily differentiated by US.

5. Evaluation of perinephric collections

   Fluid collections around the kidney may represent an abscess, urinoma, or hematoma. This situation is usually encountered with renal transplants. Determining the etiology of a fluid collection is usually not possible by US alone. A complex fluid mass is more likely an abscess or hematoma rather than a lymphocele or urinoma.

6. Renal surveillance

   Kidneys at risk for the development of specific diseases can be periodically monitored by US (e.g., the contralateral kidney following nephrectomy for Wilms tumor, evaluation of family members of patients with hereditary disorders such as polycystic disease and tuberous sclerosis). The status of existing diseases such as hydronephrosis can also be monitored to determine whether the process is static, improving, or worsening.

7. Renovascular problems

   Gray-scale US contributes little to evaluation of RAS except for measurement of renal size and demonstrating renal morphology. With color-flow Doppler, arterial and venous lesions (e.g., occlusions, stenoses, aneurysms, fistulae, malformations) of the extrarenal and intrarenal arteries and veins can be demonstrated and flow velocities estimated. The technique also allows for demonstration of bland and tumor thrombus in the renal vein and inferior vena cava in patients with renal tumors.

8. Renal transplant evaluation

   The transplanted kidney, because of its superficial position in the pelvis, is particularly well suited for US evaluation. The combination of Doppler and gray-scale sonography (duplex Doppler) makes it possible to evaluate renal allografts for such complications as rejection, RAS, and arterial or venous thrombi. Surgical complications such as hydronephrosis and lymphocele formation are also easily assessed by US.

9. Fetal renal US

   The detection of fetal hydronephrosis alerts physicians to the need for additional urologic evaluation in the early neonatal period. The availability of fetal therapy is an exciting development and still in early stages.

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### Ureter

US has limited usefulness in most ureteral disorders, except for a few instances. Dilated ureters may be seen, ureteroceles demonstrated within the bladder, and small calculi may be imaged, especially in the pelvic ureter. Color-flow demonstration of asymmetric jets of urine from the ureteral orifices in the bladder may be an indication of ureteral obstruction.

### Bladder

Uses of ultrasonography in urinary bladder evaluation include the measurement of residual urine after voiding, guidance for suprapubic aspiration, and evaluation of intravesical masses and diverticula.

### Prostate and seminal vesicles

US of the prostate is useful to estimate prostatic size. Transrectal ultrasound (TRUS) is widely used to localize a suspicious prostate lesion for transrectal biopsy. TRUS and pelvic US are also useful in the evaluation of a pelvic mass and for aspiration of cystic lesions such as seminal vesicle cysts.

### Scrotum and external genitalia

1. US is the primary imaging modality to evaluate the scrotum and its contents. It can differentiate intratesticular from extratesticular masses, and solid from cystic scrotal masses. US is also helpful when inflammation or neoplasm of the testis or epididymis is associated with a secondary hydrocele that prevents adequate palpation of the underlying lesion. Color-flow Doppler is very helpful in the scrotum and external genitalia. Perfusion patterns may help to differentiate inflammation from neoplasms and to substantiate a diagnosis of torsion or infarction.
2. Undescended testicles can often be identified in the inguinal canal (but not within the abdomen) with US. To localize cryptorchid intraabdominal testes, MRI or CT scan is usually used.
3. In male sexual dysfunction, inadequacies of flow in the cavernosal arteries are readily identified, and this technique has become a standard part of the evaluation of the impotent patient. Fibrous or calcified plaques in the tunica

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albuginea in Peyronie disease can be easily identified. In the female, translabial or endoluminal (endourethral) US has been used to identify urethral diverticula but is not favored by most urologists and radiologists over voiding cystourethrography and MRI.

### Intraoperative ultrasound

This technique is often used to assist in partial nephrectomy in patients with one or more small renal tumors. It is particularly helpful in localizing small tumors that are intrarenal with little or no exophytic component.

# Computed Tomography (CT)

## BASIC PRINCIPLES

A narrowly collimated x-ray beam is rotated about the patient, and a number of contiguous or slightly overlapping cross-sectional slices, each varying in thickness from 3 mm to 1 cm, are made through the anatomic areas of interest. Although many visceral structures can be recognized by their suggestive CT appearance, others have similar densities. To enhance structural differences, CM is frequently given. This is the same type as is used for urography and other urologic studies. Following administration of CM, multiple images are repeated. Many pathologic lesions can be recognized on the basis of their appearance before and after contrast administration. Complex computer algorithms allow reconstruction of CT data into many forms, including different planes, such as coronal and sagittal. Radiation exposure for a CT examination of the abdomen and pelvis is typically in the 10 mSv range while radiation exposure for a CT urogram varies with the number of phases obtained. The total dose for a CTU is 1.5 to two times higher than for an IVU.

## TECHNIQUE

1. Preparation is the same as for any procedure in which CM is to be administered except that a dilute mixture of barium or Gastrografin is administered orally before the CT study to identify the small and large bowels and thereby avoid confusion of fluid-filled bowel with abdominal masses or lymph nodes. In those patients being studied specifically

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for urinary tract calculi or undergoing a CTU, oral contrast material is omitted.

2. After a series of noncontrast scans through the area of interest, sections are repeated following contrast administration. CM allows better characterization and delineation of renal masses, permits evaluation of renal vein and caval patency in renal neoplasm, compares blood flow to each kidney, and helps differentiate vascular structures from solid masses, such as retroperitoneal lymphadenopathy. The contrast is usually administered as a rapid bolus using a power injector.
3. For CTU, thin sections are also obtained in the excretory phase, so that the collecting systems can be demonstrated. To distend the collecting systems and optimize detection of urothelial abnormalities, intravenous furosemide may be given during the study. Saggital and coronal reformats are performed, so that 'IVU-like' images of the urinary collecting systems can be obtained.

## COMPLICATIONS

The complications are limited to those described under contrast media. Contraindications are identical to those for IVU. Some unusually obese patients may not be candidates for CT because they cannot fit into the gantry or are too heavy for the table.

## INDICATIONS

CT plays a major role in uroradiologic diagnosis. Indications have been broadening consistently as the efficacy and utility of CT is fully appreciated. Some of its more important uses are:

1. Renal masses
    a. Diagnosis

        CT is very accurate in detecting and characterizing renal masses, identifying renal pseudotumors, and differentiating simple and complex cystic masses from solid lesions of the kidney (Figure 2-13). Because fresh blood is recognizable on CT, hemorrhagic lesions and hematomas are easily recognizable. Renal parenchymal and urothelial neoplasms also have suggestive appearances on CT. With the increasing application of CT for all manner of abdominal symptoms, there is increasing serendipitous diagnosis of small renal masses ranging in size from 1 to 3 cm. The

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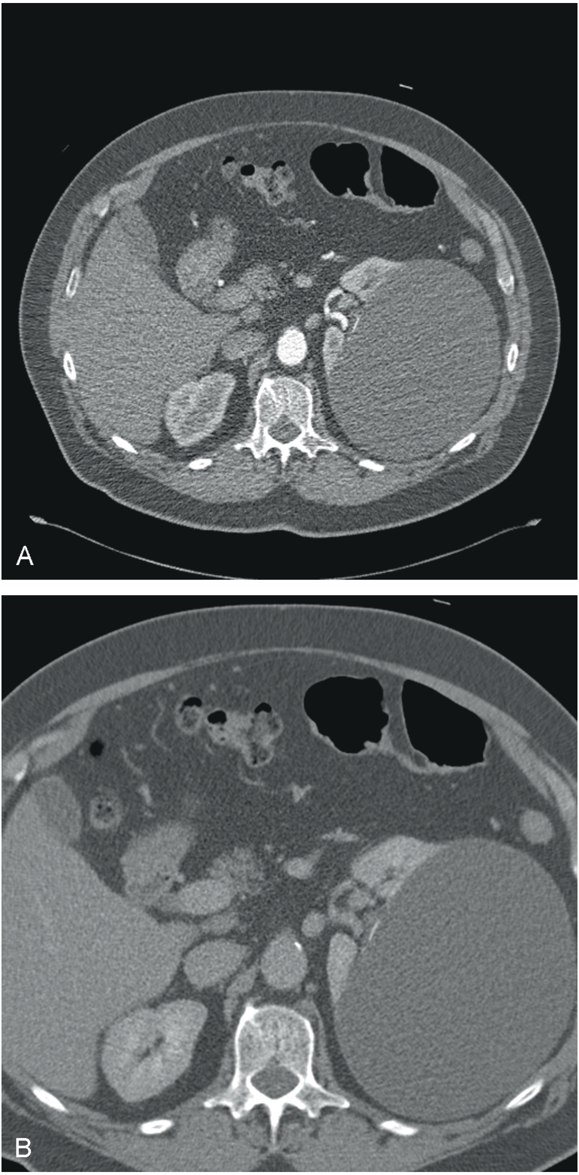

FIGURE 2-13 Left renal cyst. **A,** Arterial phase. **B,** Homogeneous nephrographic phase. The large left renal cyst does not enhance, indicating it is benign.

diagnosis of renal cancer is made when a lesion enhances after contrast administration and thus increases in density.

As smaller renal masses are diagnosed and resected, it is becoming apparent that small benign tumors, particularly small lipid-poor angiomyolipomas, may be indistinguishable from renal cell cancers (RCCs) on imaging. Percutaneous biopsy may help to establish the diagnosis preoperatively in patients who are at high risk for surgery.

b. Staging of renal neoplasms

CT is superb at demonstrating perinephric extension, evidence of renal vein or IVC tumor thrombus, regional and abdominal lymphadenopathy, and the presence of liver or adrenal metastases. It is invaluable in the preoperative evaluation of neoplasms.

c. Postoperative

CT can detect local or distant intraabdominal recurrence of neoplasm after partial or total nephrectomy for malignant disease.

d. Characterizing renal cysts

A cyst with homogeneous low attenuation (<20 HU) and thin, imperceptible walls represents a simple renal cyst (see Figure 2-13), whereas nodular enhancement of walls, thick irregular septations, and central enhancement are indicative of a malignancy. Benign cysts complicated by hemorrhage may be difficult to distinguish from malignant cystic neoplasms on CT and US. MRI is often helpful in evaluation of such indeterminate lesions because subtle enhancement of the lesion may be detectable on MRI but not on CT.

2. CT in patients with urolithiasis

The use of noncontrast CT for the evaluation of patients with acute renal colic is now accepted as the study of choice, with sensitivity and specificity for detection of renal calculi ranging between 97% and 100%. No oral or intravenous contrast is administered, and the diagnosis is available in a few minutes from the start of the scan. Definitive diagnosis requires identification of a stone in the ureter with proximal hydronephrosis. Perinephric fluid or stranding may also be seen.

Nearly all stones are dense on CT, with the notable exception being a drug calculus, as in patients on protease-inhibitor therapy for HIV infection. As CT becomes more widely used, there are numerous reports of unsuspected renal and nonrenal diagnoses that may masquerade clinically as renal colic. These include aortic aneurysms, spinal problems, renal vein thrombosis, diverticulitis, appendicitis, and acute pyelonephritis. The diagnosis of pyelonephritis and renal vein thrombosis may be difficult on noncontrast-enhanced scans and may require the administration of intravenous contrast. The increasing use of CT in the emergency room setting is raising concerns about the radiation exposure to patients with urolithiasis who have a chronic and recurrent disease and may present repeatedly with symptoms of colic. Vigilance on the part of the physicians and personnel taking care of such patients is recommended, so that patients receive no more radiation than absolutely necessary.

In pregnant patients with suspected stone disease in whom imaging confirmation is necessary, a low-dose noncontrast CT appears to be the best technique to establish the diagnosis and is preferable to a limited IVU, previously the standard imaging recommendation.

3. CT urography

   In the past several years, there has been increasing interest in using CT for a complete evaluation of the urinary tract to include evaluation of the parenchyma for masses and the urothelium for pathology. Unenhanced scans are first obtained through the abdomen and pelvis to evaluate for stones. Imaging is next performed approximately 100 seconds after the start of contrast administration to evaluate the renal parenchyma. Twelve minutes later, repeat imaging is performed through the abdomen and pelvis to evaluate the urothelium. Postprocessing is then performed, and anteroposterior and coronal oblique images which simulate an IVU are created. Intravenous diuretics promote distension of the collecting systems and are used in many institutions to optimize visualization of the collecting systems. CTU is a radiation-heavy technique, with patients receiving approximately three times the radiation dose of an IVU.

   CT is also helpful in staging transitional cell carcinoma of the renal collecting systems.

4. Renal inflammatory disease

   Most patients with acute pyelonephritis do not require imaging for confirmation of the clinical diagnosis. However, because noncontrast CT is so widely used in the assessment of patients who present with acute flank pain and suspected renal colic, patients with clinically unsuspected pyelonephritis will often have the diagnosis suggested on a CT scan. If a patient does not respond to appropriate antibiotic therapy, CT is useful in determining if complications have developed, such as a renal or perinephric abscess, and assessing inflammatory perinephric extension.

5. Hydronephrosis
   CT is superb for determining the level and etiology of hydronephrosis. The administration of oral and intravenous contrast is advisable in such patients to obtain as much information as possible.
6. Perinephric collections
   Perinephric abscess, urinoma, and hematoma can be readily recognized and often differentiated by CT.
7. Trauma
   CT is widely employed and very informative in assessing the extent of renal trauma and its possible complications, including vascular injury, extravasation from vascular system or urinary tract, urinoma formation, and impaired renal viability. When deep lacerations are identified at CT, imaging should be carried through into the excretory phase to determine if the collecting system is involved.
8. Retroperitoneal masses
   CT and MRI are the best methods of evaluating most retroperitoneal masses including neoplasms (see Figure 2-6). With very large masses, the organ of origin may be difficult to determine on axial imaging alone. The addition of coronal and saggital imaging is useful in such situations.
9. Retroperitoneal lymph nodes
   CT and MRI are the most reliable methods currently available to evaluate for enlarged retroperitoneal lymph nodes. This is an important part of the staging of many urologic tumors including those arising in the testis, bladder, and prostate. In general, retroperitoneal and iliac lymph nodes are believed to be pathologically enlarged only when the short axis diameter is more than 1 cm.
10. Retroperitoneal fibrosis
    In suspected cases of retroperitoneal fibrosis, CT can usually demonstrate the fibrous plaque. CT and MRI are the two most important diagnostic modalities in evaluating for the disease.

11. Renal transplants
    CT shares with MRI the ability to evaluate ailing renal-transplant patients for hydronephrosis and perinephric fluid collections. Azotemia precludes the use of CM to evaluate vascular integrity.

    Potential renal donors can be evaluated with cross-sectional and reconstructed CT images of renal parenchyma, vessels, collecting system, and ureters (CT, CT angiography, and CT urography).

## URINARY BLADDER

CT is valuable in staging tumors confined to the urinary bladder when the perivesical fat planes are preserved. However, perivesical stranding could be attributable to previous bladder biopsy, inflammation, or tumor, thereby limiting the staging value of CT. Enlarged lymph nodes can be detected easily on CT. MRI surpasses CT as the dominant imaging study in staging bladder cancer. Both techniques are limited, however, by their inability to detect small or microscopic metastases in normal-sized lymph nodes and minimal or microscopic tumor invasion of peripelvic fat and contiguous surfaces.

## PROSTATE AND SEMINAL VESICLES

CT enables congenital anomalies, cysts, and abscesses of the seminal vesicles to be well visualized and prostate abscesses detected. CT, however, has been replaced by MRI in assessing the prostate for most pathologies, including prostate cancer.

## ADRENAL GLAND

Adrenal masses are a common finding on abdominal CT scans, and the vast majority represent benign adenomas, even in patients with a known underlying primary malignancy. An adrenal mass that measures less than 10 HU in density on unenhanced scans is most likely to represent an adrenal adenoma, and no further workup is necessary for such a mass. Masses that are greater than 10 HU on noncontrast CT are indeterminate in nature and can represent either lipid-poor adenomas or malignant lesions. The addition of delayed imaging at 15 minutes after contrast administration is helpful in such cases. Adrenal adenomas are vascular lesions from which contrast washes out quickly. If there is greater than 66% calculated washout of contrast from a lesion, it most likely represents an adenoma.

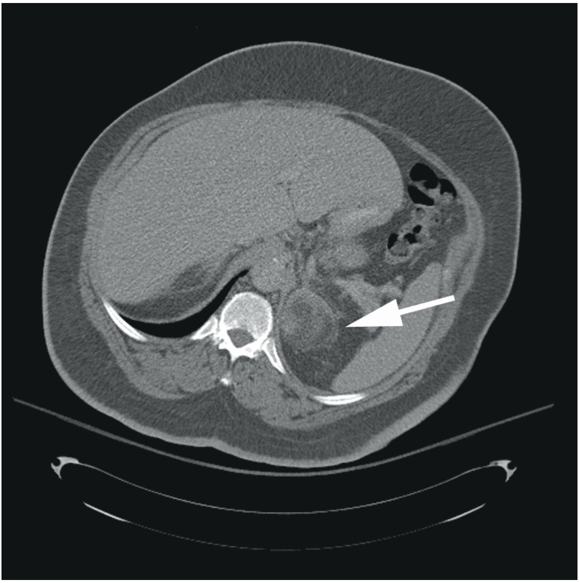

FIGURE 2-14 Left adrenal lesion *(arrow)* has low attenuation within it which represents fat, indicating that it is a myelolipoma.

Adrenal myelolipoma is a benign lesion that may contain macroscopic fat (areas with density measurements less than -10 HU) (Figure 2-14). Adrenal carcinomas are usually large lesions at diagnosis.

## MAGNETIC RESONANCE IMAGING

Magnetic Resonance Imaging (MRI) is a valuable adjunct and problem solver in imaging urinary tract pathology. The high-contrast resolution of MRI makes it valuable in tissue characterization. Current indications for MR include the assessment of a renal mass that is not characterized on other imaging studies — small degrees of enhancement within a lesion not detectable on CT may be apparent on MRI, establishing the diagnosis of neoplasm. MRI is also helpful in characterizing adrenal lesions. The use of endorectal and endovaginal coils (referred to as *surface coils*) allows high-resolution imaging of the prostate gland, seminal vesicles, urinary bladder, and the urethra. Technical details of MRI cannot be addressed in this review.

# INTERVENTIONAL URORADIOLOGY

This section will discuss commonly performed nonvascular interventional procedures in the urinary tract.

## Percutaneous Nephrostomy (PCN)

PCN refers to the percutaneous placement of a drainage catheter or access sheath into the kidney, using radiologic guidance.

### INDICATIONS FOR PCN

PCN is performed to relieve urinary obstruction, to gain access to the collecting system for therapeutic and diagnostic procedures, to divert urine to allow closure of a ureteral fistula or a dehiscent urinary-tract anastomosis, and to allow assessment of residual recoverable function in a chronically obstructed kidney. These indications are elaborated on further below.

1. To relieve urinary obstruction

   PCN is most often requested in patients in whom imaging studies demonstrate hydroureteronephrosis; these studies may indicate the etiology and the anatomic level of the obstruction. Calculus disease is responsible for obstruction in approximately one third of patients with urinary obstruction who undergo PCN, and malignancy in the rest, with carcinoma of the bladder, cervix, and colon being the most common primary tumors to cause urinary obstruction. When ureteral obstruction results in renal impairment, noncontrast computed tomography (NCCT) appears to be the best imaging modality to identify calculus causes of obstruction whereas magnetic resonance urography (MRU) is superior for identifying noncalculus causes of obstruction. In patients with normal renal function, contrast-enhanced CT can identify the presence and cause of hydronephrosis in nearly all cases. MRU is particularly helpful in delineating the anatomy in patients with urinary diversion to bowel conduits.

   It is important to attempt, or at least consider, the periurethral retrograde approach for renal drainage (ureteral intubation with cystoscopic guidance) in a patient with urinary obstruction before resorting to a PCN. Percutaneous drainage should ideally be reserved for patients in whom retrograde attempts are either unsuccessful or not feasible.

In patients with obstruction, accompanied by signs or symptoms of urosepsis, PCN drainage provides rapid decompression of the obstructed collecting system and defervescence of the urosepsis. However, when obstruction and infection are due to renal or ureteral calculi, retrograde ureteral drainage is as effective in draining the collecting system as is PCN. In these cases, the decision to perform PCN or retrograde ureteral catheter drainage should be made by assessing what the best therapy for the stone would be. For instance, patients who have large renal calculi that would be best managed by percutaneous methods should have a PCN performed; patients with smaller ureteral calculi that would be amenable to SWL should be drained by a ureteral catheter placed by a retrograde periurethral approach with cystoscopic guidance (see Figure 2-12).

PCN drainage can help to preserve or improve renal function until the cause of obstruction can be relieved in patients in whom the obstruction is expected to respond to treatment, such as chemotherapy, radiation therapy, or surgery. For patients with terminal malignancies and bilateral obstruction in whom ureteral stents cannot be placed, unilateral PCN drainage is usually preferred to bilateral drainage to avoid the inconvenience of two externally draining nephrostomy bags. Unilateral drainage suffices in most patients to maintain renal function at an acceptable level and the less affected kidney (as judged by less hydronephrotic changes or parenchymal atrophy on imaging studies) is chosen for drainage (Figures 2-15 and 2-16).

2. To gain access to the collecting system

   PCN is often just the first step in performing a variety of other interventional procedures in the kidney and ureter. Some examples of procedures that can be performed through a PCN track include the treatment of renal or ureteral calculi (stone fragmentation, removal, or chemolysis), ureteral interventions such as stricture dilation or stent placement, retrieval of foreign bodies such as fractured stent fragments, nephroscopic surgery such as endopyelotomy for UPJO, and brush biopsy or percutaneous therapy of urothelial tumors. Interventions can often be done at the

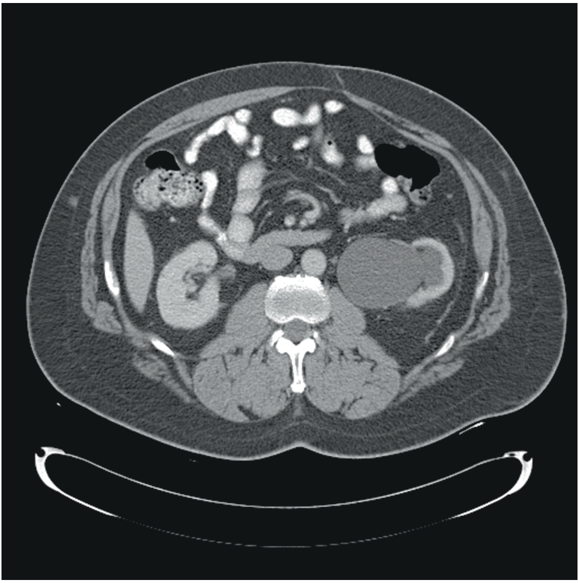

FIGURE 2-15 CT shows chronic hydronephrotic atrophy of left kidney due to colon cancer. Patient developed right hydronephrosis a few months later, necessitating a right nephrostomy.

same sitting as the PCN if the procedure is not complicated by excessive bleeding and if there is no infection.

3. To divert urine

   PCN is often performed to divert the urine to allow closure of a ureteral fistula, ureteral leak, or a dehiscent urinary tract anastomosis. PCN drainage alone is rarely successful in totally diverting the urine; the addition of ureteral stenting is usually required to bridge leaking ureteral segments or dehiscent anastomoses, whereas ureteral occlusion is usually necessary in patients with intractable fistulae, most commonly vesicovaginal fistula. Urine diversion by PCN alone has been used with some success to treat patients with intractable hemorrhagic cystitis.

4. To assess residual renal function

   Renal drainage by PCN may allow assessment of residual recoverable function in a chronically obstructed kidney

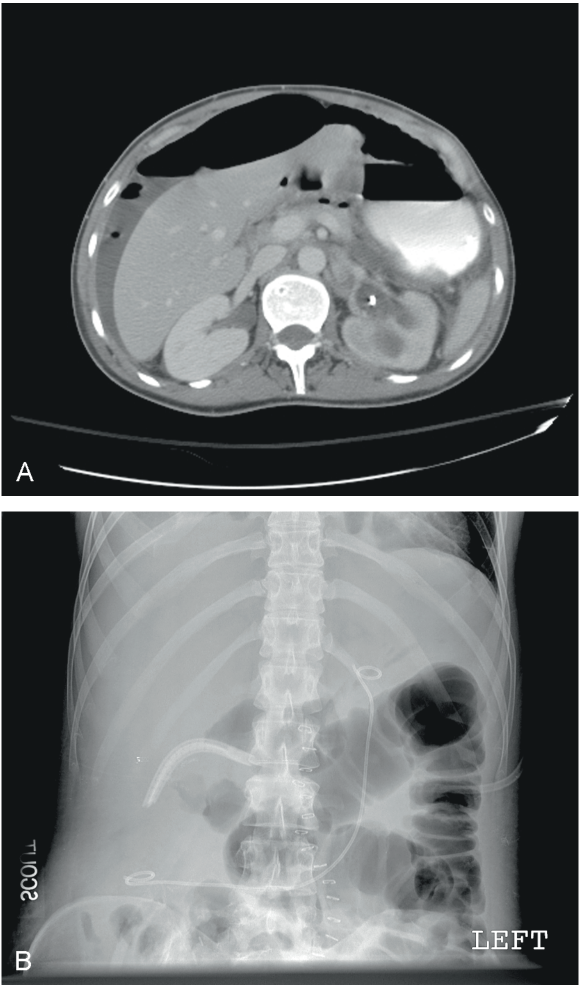

FIGURE 2-16 Percutaneous nephrostomy in patient with continent urinary diversion and occluded internalized stent. **A,** CT shows left-sided obstruction with delayed nephrogram. **B,** Abdominal film demonstrates an internalized stent in the continent pouch. Patient was febrile with urinary tract infection. The distal end of the stent could not be found even with pouch-endoscopy in the operating room.

(*Continued*)

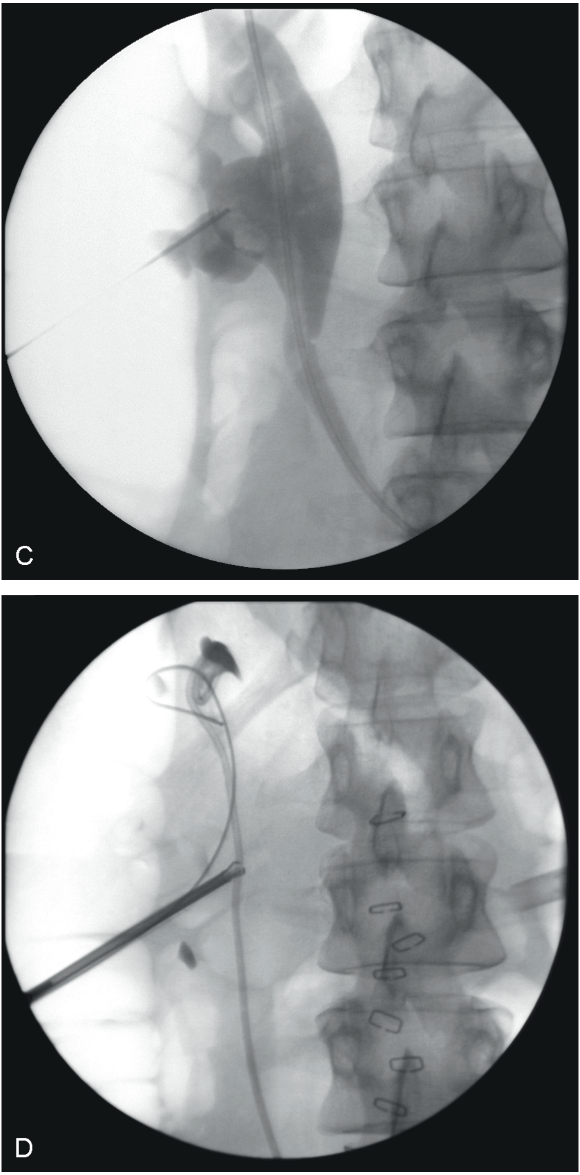

FIGURE 2-16, cont'd **C,** Percutaneous nephrostomy of the hydronephrotic left kidney. Patient was allowed to defervesce for a few days. Grossly purulent urine was aspirated. **D,** When patient was afebrile, the left ureteral stent was removed through the nephrostomy track.

that appears to be either nonfunctioning or poorly functioning. The presence of renal parenchymal atrophy on CT or renal US does not necessarily predict a poor potential for functional recovery after drainage with a PCN, although a kidney that is reduced to a hydronephrotic shell is unlikely to recover function significantly.

## PREPROCEDURAL EVALUATION PRIOR TO PCN

Preprocedural evaluation in patients being considered for PCN includes a clinical history to identify a potential bleeder and routine laboratory tests of coagulation and renal function. This is discussed further in the section on contraindications to the procedure.

Prophylactic antibiotics are beneficial in decreasing the development of sepsis in both high-risk patients (e.g., those with struvite stones, diabetes, urinary tract obstruction, indwelling catheters, previous manipulation, instrumentation of the urinary tract) and in patients with a low risk for developing sepsis. Antibiotics should be administered in such a way that maximum blood levels are attained during the procedure, immediately prior to or less than 2 hours before the procedure, and should be continued after the procedure for 24 to 48 hours in low-risk groups and for 48 to 72 hours in high-risk groups. In patients with urinary obstruction, antibiotic therapy should be continued until satisfactory renal drainage is assured to avoid postprocedural bacteremia.

The risk of periprocedural sepsis is increased in the elderly, diabetics, and in patients with indwelling catheters, stones, ureterointestinal anastomosis, or the clinical presence of infection; septic shock can occur in as many as 7% of patients with pyonephrosis. The organisms that commonly infect the genitourinary tract are gram-negative rods and include *Escherichia coli, Proteus, Klebsiella*, and *enterococcus*. Antibiotic prophylaxis ideally should be based on culture results. For patients with obstruction and overt clinical infection in whom a specific organism has not yet been identified, broad-spectrum antibiotic therapy active against the common urinary pathogens is prudent.

## CONTRAINDICATIONS TO PCN

The only absolute contraindication to PCN is the presence of an uncorrectable bleeding disorder; however, if the bleeding diathesis is due to a coagulopathy caused by urosepsis, urinary drainage will be necessary before the bleeding abnormality can be corrected.

Correction of abnormal coagulation is needed if the international normalized ratio (INR) and the activated partial thromboplastin time (PTT) are greater than 1.5 times above the normal range; standard protocols are used for this. Platelet transfusion will correct drug-induced prolongation of the bleeding time if needed. Platelet counts greater than 50,000/dL are a safe value for most patients.

PCNs are often performed as an inpatient procedure but may be performed on an outpatient basis. Patients who may not be suitable candidates for outpatient PCN include those with hypertension, untreated urinary tract infection, coagulopathy, and staghorn calculi because these patients may be more likely to have complications such as procedure-related sepsis or bleeding.

## TECHNIQUE

1. Monitoring of patients

   Continuous electrocardiogram monitoring during the procedure is advisable. Large-bore and secure intravenous access should be routinely established before the procedure so that intravenous sedation and analgesia can be administered during the procedure and intravenous access is readily available if other medications need to be administered. Intravenous sedation combined with local anesthesia is sufficient to keep most patients comfortable; such patients require transcutaneous oximetry.

2. Localization of collecting system

   The renal collecting system is localized by US if it is hydronephrotic. In a moderately or severely dilated collecting system, US guidance is successful in aiding entry into the collecting system in 85% to 95% of patients; conversely, in mildly dilated collecting systems, the success rate may be as low as 50%.

   Fluoroscopic guidance is used for the procedure if a radiopaque stone can serve as a target for puncture, or if the collecting system can be opacified with contrast. If renal function is normal (as in a patient with a urinary fistula), the collecting system can be opacified with contrast excreted after intravenous administration. Opacification of the collecting system by injecting through a retrograde catheter is helpful in patients with nonopaque calculi, for planned percutaneous endopyelotomy, and in patients with nondilated collecting systems and urinary stones. Blind punctures of the kidney using anatomic landmarks are apt to require multiple punctures for optimal entry and should be measures of last resort; ultrasound guidance can facilitate appropriate and safe puncture of the collecting system with the fewest number of sticks.

3. The patients are positioned in either a prone or a prone oblique position with the ipsilateral side elevated 20 to 30 degrees; however, if the patient cannot lie prone, the procedure can be performed in a supine oblique position.

   CT guidance is particularly helpful in this case. Initial puncture can be performed with CT guidance, and the subsequent manipulations for catheter placement are performed with fluoroscopic guidance. Preprocedural CT or MR scanning is necessary and highly recommended in patients with aberrant anatomy (e.g., severe scoliosis, congenital abnormalities) so that the relationship of the kidney to the liver, spleen, colon, gallbladder, and pleural space can be determined.
4. The flank is cleansed, and a subcostal skin entry site in the posterior axillary line is anesthetized. A needle is advanced into the collecting system from the flank, urine aspirated, contrast material injected, and a guidewire inserted through the needle into the kidney. The procedure is monitored fluoroscopically.
5. The needle is removed and the nephrocutaneous track enlarged by passing fascial dilators over the guidewire.
6. A drainage catheter, usually an 8 French "pigtail" catheter with a self-retaining mechanism, is passed over the guidewire and positioned in the renal pelvis. The guidewire is removed and the catheter secured to the skin and attached to a closed gravity drainage bag.

## RESULTS

1. A PCN catheter can be successfully placed in 98% to 99% of patients with obstructed kidneys and dilated collecting systems.
2. Nondilated collecting systems or complex stone cases are technically challenging, with reported success rates of catheter placement in 85% to 90%.
3. When obstruction is complicated by urosepsis or azotemia, the response to renal decompression is marked and often immediate, with fever and flank pain improving in 24 to 48 hours after PCN drainage. As mentioned earlier,

when obstruction and infection are due to ureteral calculi, retrograde ureteral catheterization and PCN are equally effective in relieving the obstruction and infection; neither technique is superior to the other in promoting rapid drainage or clinical defervescence.

4. In patients with azotemia secondary to obstruction, PCN returns renal function to normal or near normal levels in 7 to 14 days and can improve renal function enough to obviate dialysis in 28% to 30%. In patients with malignancies, the ureters can be obstructed by contiguous involvement or extrinsic compression. The need for external nephrostomy drainage is often permanent in such patients because ureteral stents often fail in adequately draining patients with extrinsic obstruction. Long-term survival after palliative diversion for malignant ureteral obstruction is poor, with only 25% of patients alive at 1 year. Our approach in patients with bilateral obstruction due to malignancies is to initially drain the symptomatic side, if there is one, or drain the kidney which appears to have more preserved renal parenchyma as gauged by cross-sectional imaging. The contralateral kidney is drained only if there is suspected infection, or if unilateral drainage does not improve renal function enough to administer the necessary chemotherapy.

## COMPLICATIONS

1. The overall serious complication rate of PCN is low, with a mortality of 0.2% compared to a surgical mortality of 6%. Major complications include hemorrhage and sepsis.
2. Hemorrhage requiring transfusion or other therapy is a complication in less than 1% to 2.4% of patients and is related to renal arterial pseudoaneurysms or arteriovenous fistulas due to laceration of lobar arteries. Most hemorrhage associated with nephrostomy placement is transient and self-limited; it is not uncommon to have pink or slightly bloody urine drainage for several days after a nephrostomy, and this is not considered a complication. Serious vascular trauma is suspected if the urine continues to be grossly bloody after 3 to 5 days, if new intrapelvic clots are observed on nephrostograms, or if there is a significant drop in the hematocrit. If the drop in the hematocrit is out of proportion to the urine blood loss, a retroperitoneal hematoma should be suspected

and a CT scan obtained. Angiography and possible arterial embolization should be considered in patients who have significant continuous or recurrent bleeding for longer than 4 to 5 days after PCN placement.

3. Sepsis after nephrostomy tube placement can occur, particularly in patients with stone disease. Patients with pyonephrosis are more prone to this complication and may develop postprocedure fever or even septic shock, despite the use of aminoglycoside prophylaxis. Forceful opacification of the collecting system to visualize the site and cause of obstruction should be deferred in all patients with urinary obstruction until the collecting system has been adequately decompressed for 24 to 48 hours and the patient is afebrile.
4. Inadvertent injury of adjacent organs is uncommon. The colon may lie posterior or posterolateral to the kidney and can be entered during a PCN. Retrorenal position of the colon is more common in patients who are thin and have little retrorenal fat, who have colonic dilation, or have abnormal anatomy such as marked kyphosis or scoliosis. When doubt about safe access exists, preprocedure CT to delineate the anatomy is prudent. The complication can often be managed conservatively, with drainage of both the kidney and the colon by separate catheters until the nephrocolic fistula heals.
5. An intercostal approach (often required for access to the upper poles of the kidneys) causes more thoracic complications than a subcostal puncture. In expiration, a posterior intercostal approach between the eleventh and twelfth ribs poses little risk of injury to the spleen and liver, but the lungs remain vulnerable to puncture in many patients. Other thoracic complications include pleural effusion, pneumonia, atelectasis, hydrothorax, and pneumothorax.
6. Minor complications that may occur are catheter dislodgment and urine extravasation. Dislodgement is more common in obese patients and in disoriented patients and can be minimized by using self-retaining drainage catheters, routinely exchanged every few months. Dislodgement in the first week after placement often necessitates a fresh track. Renal pelvic perforation is unusual in a routine PCN performed for drainage of an obstructed collecting system and is more likely to occur in patients with large staghorn stones. It is usually a self-limiting complication.

## PERCUTANEOUS NEPHROSTOMY FOR NONOBSTRUCTIVE INDICATIONS

### Management of upper urinary tract calculi

Percutaneous management of urinary tract calculi is indicated in patients who are not candidates for SWL or ureteroscopy. Percutaneous techniques are also used to salvage SWL or ureteroscopic failures. SWL is the treatment of choice for most renal and ureteral calculi. Stone-free success is greatly influenced by the stone size, with stones that are 1 cm or less in size representing the ideal for SWL. Stone-free rates of 85% to 87% have been reported for stones that are 1 to 2 cm in size. Distal ureteral calculi are managed by retrograde ureteroscopy or, in select cases, extracorporeal SWL.

**Stone size:** In patients with large calculi, over 2 to 3 cm in size, SWL has a poor chance of complete success, a high probability of requiring adjunctive therapy, and a significant incidence of complications. With stones larger than 2.5 to 3 cm, only 30% to 35% of patients may be stone-free with SWL, compared to 70% to 90% of those treated with percutaneous nephrostolithotomy (PCNL).

**Staghorn stones:** The primary approach to these stones should be by PCNL. Branched staghorn stones that fill the majority of the collecting system pose special problems because stones may be located deep in infundibula and calices that may be difficult to reach from the initial percutaneous tract. PCNL is initially used to rapidly remove large volumes of easily accessible stone with ultrasonic or electrohydraulic lithotripsy ("debulking"). If infundibulocaliceal fragments are inaccessible from the nephrostomy tract using the usual endourological techniques, SWL is used to break up the small volumes of remaining stones, followed by PCNL to remove the residual fragments.

**Urinary obstruction, compromised urinary drainage:** Urinary stasis can predispose to calculus formation. The most common examples of stones in association with obstruction are in ureteropelvic junction (UPJ) obstruction, caliceal diverticula, malrotated kidneys, ectopic kidneys, horseshoe kidneys, and obstruction due to renal cysts or other renal masses. Although SWL can successfully break up the symptomatic calculi in these situations, the fragments are unlikely to be able to successfully pass even if the stone debris is adequately fragmented. In these cases, percutaneous stone therapy is combined with endourologic treatment for the underlying obstructive process, such as endopyelotomy for UPJ stenosis or balloon dilation for infundibular or ureteral strictures.

**Stone composition:** The composition of a calculus is critical to decide on the best method of management. Certain calculi (e.g., cystine calculi) are readily fragmented by ultrasonic lithotripsy but are refractory to SWL, making PCNL the treatment of choice. On the other hand, uric acid calculi respond well to SWL but not to ultrasonic lithotripsy. For stones larger than 2 cm, proceeding directly to PCNL is the best option. All stone material must be removed at the time of the percutaneous procedure to ensure that the patient will remain stone-free.

Stones composed of calcium oxalate dihydrate and struvite break up well with SWL or any other form of power lithotripsy, whereas stones composed either partially or completely of calcium oxalate monohydrate do not respond well to SWL. With these stones, the volume of the stone is the main determinant of the most desirable mode of therapy.

Stones that do not adequately fragment with SWL or are inaccessible by ureteroscopy require a PCN for percutaneous ultrasonic lithotripsy. PCNL is also indicated in patients in whom certain removal of a stone is important (such as airline pilots) because residual stone fragments persist in a significant percentage of patients following SWL.

## TECHNIQUE FOR PERCUTANEOUS NEPHROSTOLITHOTOMY (PCNL)

Two primary components in the percutaneous therapy of upper urinary tract calculi are the establishment of an access tract and the actual stone removal itself. Accurate access is the essential underpinning of a successful PCNL because a poorly placed track may make it impossible to remove even the most accessible of calculi. Fluoroscopic control is usually preferred for the procedure, especially if the calculi are radiopaque. CT is useful in preprocedural planning in patients with aberrant anatomy, so that the liver, spleen, colon, and pleural space can be avoided by the proposed track. If the calculi are faintly opaque or the collecting system is not dilated, placement of a retrograde catheter prior to the puncture is invaluable and allows both opacification and distension of the collecting system. Local anesthesia and intravenous sedation are generally sufficient for establishing the track.

Subsequently, track dilation and stone extraction are performed in the operating room. Experience has proven that tracts can be dilated acutely to 24 to 30 French with no adverse effects. After the procedure, the collecting system is inspected to ensure a stone-free state. It is standard practice to leave in a large bore nephrostomy tube after the procedure to provide reliable drainage of urine, tamponade the track and allow the renal puncture to heal, and permit access to the collecting system if additional procedures are required, although many endourologists place small-bore catheters or only a ureteral stent following the stone removal. The nephrostomy catheter is removed in 48 hours to 1 week, after a nephrostogram demonstrates no leaks from the collecting system and no residual stones.

When the calculus is located in a calix or diverticulum, access should be obtained through that particular calix or diverticulum.

## CONTRAINDICATIONS

An uncorrected bleeding abnormality is the only absolute contraindication. The procedure should not be performed if a stone-bearing kidney is uninfected and nonfunctioning. A relative contraindication is the inability to establish a safe access track.

## COMPLICATIONS

1. Bleeding

   Significant arterial bleeding occurs in 0.5% to 1.5% of patients. Vascular injury during the placement of the access track or track dilation can lead to pseudoaneurysms, arteriovenous fistulas, perinephric hematomas, and loss of functional parenchyma. Initial puncture into a calix, rather than an infundibulum or the renal pelvis, is the least likely to cause major vascular injury and is the preferable site of puncture. If excessive bleeding occurs during or after PCNL, the nephrostomy tube can be clamped to tamponade the track and the collecting system. If that fails, a larger nephrostomy catheter can be placed, which will tamponade the track better and also allow blood clots and residual calculus fragments to pass. Selective angiography and embolization should be considered if the above measures fail.

2. Injury to adjacent organs

   The colon can be nicked if it is positioned posterior to the kidney. The colonic injury may not be obvious until the postprocedure nephrostogram demonstrates colonic filling with contrast. If the nick is small, the injuries can be managed conservatively by draining the kidneys with a double-pigtail ureteral stent placed from below, pulling the nephrostomy tube into the colon, and leaving it to act as a colostomy tube. The track usually seals in a few days. If a more serious injury occurs, open repair may be required.

   Injury to the duodenum, liver, and spleen are uncommon. Pleural and lung injuries may occur with supracostal punctures.
3. Sepsis

   PCNL is considered to be a clean-contaminated procedure in patients with sterile urine preoperatively, but a rise in temperature is common after stone removal. Postoperative bacteremia can occur, and some of the factors affecting the development of postoperative fever are the duration of surgery and the amount of irrigant fluid.
4. Perforation

   During the process of stone removal, the renal pelvis can be perforated by a sharp fragment of stone or by one of the instruments (such as the ultrasound probe) in as many as 10% of cases. Most such perforations heal within 12 to 24 hours as long as good urine drainage is maintained. Serial nephrostograms will show that even sizable renal pelvic and ureteral lacerations heal in a few days without stricture formation.

   A calculus can extrude through a urothelial tear. Renal pelvic extrusions should be treated with nephrostomy drainage, whereas ureteral tears should be treated with stenting for a few weeks. In the absence of infection, extrusion of calculus material into the perinephric and periureteral tissues appears to be of no clinical consequence.

## TREATMENT OF URETERAL CALCULI

SWL is the treatment of choice for upper ureteral calculi and has higher success rates if the stone can be pushed back into the kidney. These calculi can also be approached in a percutaneous, antegrade fashion. In the midureter, most authorities favor ureteroscopic extraction of calculi or retrograde displacement of the calculus into the kidney followed by SWL.

For distal ureteral stones, ureteroscopic extraction is probably the technique of choice because of its high initial success rate, the rare need for secondary treatments and postureteroscopic interventions, and the low complication rate of ureteroscopy in the distal ureter.

Ureterolithotomy for stone removal is unusual and performed on the rare occasion for stones that are impacted or embedded in the ureter and require open surgical removal.

### OTHER PROCEDURES PERFORMED THROUGH A PCN ACCESS TRACK

In patients with **UPJ obstruction**, PCNL can be often combined with an endopyelotomy. The percutaneous route is also well suited to the **removal of foreign bodies** (e.g., broken stents, guidewire fragments, internal ureteral stents, fungus balls) from the renal pelvis and/or ureter. Stents that have not been changed in the recommended period may encrust, become brittle, and fracture; fractured are best approached with a combined percutaneous-endoscopic technique.

## Ureteral Stenting

### PRINCIPLES

1. Percutaneous ureteral stenting provides urinary diversion without the need for an external collection device when retrograde insertion of a ureteral stent is not possible or practical.
2. Most patients find a ureteral stent catheter more acceptable and convenient than a nephrostomy catheter.

### INDICATIONS

1. Long-term stenting (months to years) is most frequently performed to bypass a ureteral obstruction.
2. Short-term stenting (weeks to months)
   a. Facilitates healing of postoperative or traumatic pyeloureteral leaks or ureteral fistulae by diverting the urinary stream
   b. Prevents stricture formation as ureteral injuries or implantations (native or allograft ureters) heal by providing a mold around which ureteral epithelialization is facilitated
   c. Maintains ureteral caliber following balloon dilation or incision of benign ureteral strictures

3. Catheters percutaneously placed into the ureters facilitate intraoperative ureteral identification during difficult surgical dissections (e.g., revision of an obstructed ureteroileal diversion).

## CONTRAINDICATIONS

1. The presence of active renal infection
2. Markedly diseased bladder that would be intolerant of a stent (e.g., radiation cystitis, bladder invasion by adjacent neoplasm)
3. Bladder fistulae

## TECHNIQUE

1. Following PCN, a guidewire and catheter are manipulated through the abnormal (often stenotic) ureteral segment into the urinary bladder, or bowel conduit, or urinary reservoir.
2. The catheter is replaced with a ureteral stent in which multiple side holes have been created where the stent will eventually be positioned in the renal pelvis. Kidney urine enters the stent through these side holes, travels through the catheter, and exits from its distal pigtail segment. Depending on ureteral caliber, urine may also flow around the stent. The proximal end of the stent protrudes from the skin and is obturated externally. This is an external ureteral stent catheter.
3. An external ureteral stent can be periodically changed from the flank over a guide wire.
4. Urinary drainage can be totally internalized by placing an internal ureteral stent with a pigtail configuration at both ends. The proximal pigtail is positioned in the renal pelvis and the distal pigtail in the bladder. Double pigtail stents must be periodically changed (at least every 6 months) cystoscopically.
5. Patients who require ureteral stenting following ureteral diversion to a bowel conduit should have an external ureteral stent inserted in combined antegrade/retrograde fashion. A guide wire and catheter are first manipulated beyond the abnormal ureteral segment, through the bowel conduit, and out the stoma rather than into the bladder. The catheter is removed, and a single pigtail drainage catheter is passed retrograde into the renal pelvis. The distal end of this catheter protrudes through the stoma to drain into the urostomy collection bag. Internal ureteral stents should not be used in patients with ureteroenterostomies or continent urinary diversion reservoirs.

6. If retrograde endoscopic attempts to pass catheters beyond ureteral obstructions and fistulae are unsuccessful, fluoroscopically guided retrograde periurethral catheter manipulations are often successful in the radiology department. This approach employs standard interventional equipment (e.g., catheters, guide wires, sheaths) passed through or over partially inserted ureteral catheters.

## RESULTS

1. Both internal and external ureteral stents allow patients to lead as active a life as their underlying condition will permit.
2. Ureteral obstructions can often be negotiated in antegrade (percutaneous) fashion even if retrograde cystoscopic catheterization is not possible (e.g., neoplastic obstruction of a ureteral orifice, distal ureteral angulation secondary to prostatic enlargement, spread of prostatic malignancy, ureteral reimplantation, tight ureteral stenoses, urethral stricture).
3. Approximately 85% to 90% of ureteral obstructions and fistulae can be stented percutaneously. Very tightly obstructed ureters and ureters that are both tortuous and encased by tumor or fibrosis are the most frequent causes of failure of antegrade stent placement.
4. Internal ureteral stents may not drain kidneys as well as a PCN, especially when ureteral obstruction is caused by extrinsic compression or if intravesical pressure is elevated at rest or during micturition.

## COMPLICATIONS

1. Improperly positioned stents will not provide optimal urinary drainage. This problem can be rectified with percutaneous, cystoscopic, or ureteroscopic techniques. Proximal stent migration can lead to perforation of the renal pelvis or calyces, which can result in a urinoma or even catastrophic exsanguination due to erosion of the stent tip into a renal vessel. Stents that have migrated up into the kidney above a lower ureteral stricture or anastomosis can be extracted through a nephrostomy track under fluoroscopic guidance. A second approach is to use ureteroscopy to reposition the caudal end of the stent within the bladder. A stent that is positioned too far cephalad (so that the distal end is no longer within the urinary bladder) is usually related to placement of too short a stent rather than to cephalad migration.

2. Symptoms attributable to the intravesical coil of the stent (even when properly positioned) occur commonly, including microscopic hematuria, pyuria, lower abdominal pain, dysuria, urinary frequency, nocturia, and flank pain on voiding (due to renal reflux of bladder urine).
3. Fatigue fractures and encrustation of ureteral stents may occur if stents are not periodically replaced. This should be carried out at least every 6 months and more often in patients who form stones.

## Dilation of Ureteral and Urethral Stenoses

### PRINCIPLES

1. Chronic ureteral stenting is not the optimal therapy for benign postoperative ureteral strictures, although it may be appropriate for malignant ureteral obstructions.
2. Many benign ureteral strictures are amenable to balloon catheter dilation or endourologic incision.
3. These procedures, if successful, can spare patients the nuisance of chronic indwelling stents or the risks of additional surgery.

### INDICATIONS

1. An attempt at balloon catheter dilation of all benign ureteral strictures should be made before relegating patients to additional surgery or to chronic PCN or indwelling ureteral stent drainage.
2. Endoscopic incision, employed alone or in combination with balloon dilation and ureteral stenting, can relieve certain ureteropelvic junction (UPJ) obstructions (both congenital and acquired) and postoperative ureteroenteral anastomotic strictures.
3. Balloon dilation of ureters encircled by sutures sometimes results in disruption of the offending ligature, thus saving the patient an operation.
4. Balloon dilation of vesicourethral anastomotic strictures that develop after radical prostatectomy is a nonoperative alternative to endoscopic incision and appears to be less likely to cause urinary incontinence.

## CONTRAINDICATIONS

1. Ureteral strictures caused by malignant disease, either primary or recurrent
2. Inflammatory or traumatic urethral strictures appear to be more amenable to optical internal urethrotomy than to balloon dilation.

## TECHNIQUE

1. The strictured ureter is cannulated as described above.
2. Biopsies and/or other imaging studies are obtained to confirm that the stricture is of benign etiology.
3. A catheter with an inflatable balloon capable of withstanding high pressure (15 to 17 atmospheres of pressure) and inflated diameter of 6 to 10 mm (18 to 14 French) is used. Ureteral stenoses are generally inflated to 6 to 8 mm, whereas urethral stenoses are dilated with 8- to 10-mm balloons (24 to 30 French). The catheter is advanced across the stricture and the balloon inflated with diluted contrast material. A waist or narrowing is seen initially in the inflated balloon at the stricture site which should disappear with continued or repeated inflations if the balloon dilation is technically correct.
4. Following dilation, a ureteral stent is placed, which remains in situ for 6 to 8 weeks to maintain luminal patency while the ureteral musculature heals. Stenting is accomplished with the largest catheter that can be comfortably accommodated. This is generally 10 French if the stent traverses the intramural ureter, but it may be larger if a ureteroenterostomy stricture is dilated and stented.
5. After 6 to 8 weeks, the stent is exchanged for a PCN, and the efficacy of the dilation is assessed by a nephrostogram and urodynamic studies prior to catheter removal.
6. If the ureteral stricture has been dilated and stented in a retrograde fashion per urethra with an internalized double pigtail catheter (usually 7 to 8 French in size), assessment of efficacy of balloon dilation is performed with an IVU obtained at 1, 6, and 12 months after stent removal.
7. Similar techniques have been adapted to treat congenital UPJ obstructions by balloon dilation, endoscopic incision, and stenting.

### RESULTS

1. Approximately 58 percent of all benign ureteral strictures can be successfully dilated with balloon catheters, usually with one attempt.
2. If there is poor response to the first attempt at balloon dilation, a second attempt at balloon dilation is worthwhile because some strictures will respond favorably to a second similar procedure.
3. The etiology and age of the stricture seem to influence the outcome of dilation therapy. Strictures not associated with ischemia or dense fibrosis may be successfully dilated (including those that occur in renal allograft recipients). Those associated with radiotherapy or surgical devascularization have a much lower rate of success. Strictures that have been present for less than 3 months respond much better to dilation therapy than do those that are more chronic in nature.
4. Endoscopic incision followed by balloon dilation and ureteral stenting is more effective than balloon catheter dilation alone for ureteroenteral anastomotic strictures and UPJ strictures.
5. Unsuccessful balloon dilation does not adversely affect other therapeutic options, including chronic indwelling ureteral stenting, surgical revision, or insertion of a metallic expandable ureteral stent (Wallstent or similar device). Although favorable short-term results have been reported with metallic ureteral stents, the long-term efficacy of metallic stents has not been stellar.

### COMPLICATIONS

No known permanent sequelae have resulted from unsuccessful dilation therapy. Laceration of ureteral mucosa or wall may occur with balloon dilation. These perforations heal uneventfully if the ureter is adequately stented and probably do not affect the outcome of dilation therapy.

## Percutaneous Drainage of Renal and Related Retroperitoneal Fluid Collections

### PRINCIPLES

Percutaneous drainage of renal and related retroperitoneal abscesses almost always obviates the need for surgical drainage. Cross-sectional imaging is used for guidance for the drainage.

## INDICATIONS

Renal abscess or infected renal cyst that fails to improve with broad-spectrum antibiotics or a large infected renal or retroperitoneal fluid collection that requires drainage.

## CONTRAINDICATIONS

1. Absence of a safe percutaneous drainage route
2. Small renal abscesses (less than 3 cm in diameter) can often be effectively treated with a course of intravenous antibiotics and may not require drainage.
3. Abnormal coagulation parameters

## TECHNIQUE

1. The anatomic relationship of the fluid collection to its surrounding structures is assessed by cross-sectional imaging (CT or, less commonly, US). A safe, extraperitoneal route that avoids puncture of viscera, pleura, and major vessels is planned for diagnostic needle aspiration and catheter placement.
2. Diagnostic aspiration is performed with a 20- or 21-gauge needle to confirm the diagnosis.
3. If diagnostic aspiration yields infected material, a catheter is introduced into the collection under fluoroscopic control, the abscess drained completely, and the catheter securely sutured in place to provide continuous drainage. Injection of contrast medium (to evaluate the size and appearance of the abscess and assess whether it communicates with the collecting system) is minimized at the time of the drainage to reduce the chances of inciting bacteremia or septic shock.
4. Septa within an abscess can usually be perforated with catheters and guide wires so that locules intercommunicate. Even so, multiloculated abscesses may require more than one catheter for complete drainage.
5. Multiple drainage catheters may be needed for renal abscesses that have spread retroperitoneally (one catheter for each component). Abscesses associated with ureteral obstruction require a PCN catheter in addition to the abscess drainage catheter.
6. Abscesses related to the urinary tract have less viscous contents than those that originate from the pancreas or

gastrointestinal tract. Gravity drainage with 10 to 14 French pigtail or Malecot catheters is effective in draining most urinary tract abscesses. If the abscess contents are very viscous, large sump catheters placed to suction and periodic irrigation with saline may be required.

7. When there is clinical defervescence to the percutaneous drainage, patients can be switched to oral antibiotics from parenteral therapy, discharged from the hospital with their drainage catheters in place, and followed as outpatients. Periodic follow-up catheter studies and CT scans are usually obtained at 1- to 2-week intervals to ensure that the catheter remains patent. Follow-up CT scans also demonstrate if undrained locules exist.
8. If a patient fails to improve on antibiotics and catheter drainage, a CT scan is obtained to detect undrained locules, enteric communications, or misplaced catheters.
9. Indications for catheter removal include the following:
    a. A satisfactory clinical response with defervescence of clinical signs of infection
    b. Return of white blood cell count to normal
    c. Cessation of drainage
    d. Obliteration of the abscess cavity
10. Drainage catheters usually need to remain in place for an average of 2 to 4 weeks for most urinary abscesses. Renal abscesses usually resolve in less time than those that have spread extrarenally. The track will close following catheter removal if all infected material has been evacuated. Perinephric abscesses are often associated with an underlying abnormality such as stones or strictures that have to be treated after the abscess has resolved.

## RESULTS

Percutaneous abscess drainage can be expected to cure approximately 72 percent of renal and related retroperitoneal abscesses. This is a significant improvement compared to the results of surgical drainage and is due to the use of cross-sectional imaging techniques for evaluation, which allows the diagnosis of abscesses earlier in their development, needle aspiration to confirm the nature of a fluid collection, and also the efficacy of percutaneous drainage techniques.

## COMPLICATIONS

1. Many patients develop transient bacteremia, febrile episodes, and even septic shock after percutaneous abscess drainage. These complications can be minimized by limiting catheter manipulation, lavage of the cavity, and/or contrast opacification of the abscess at the time of drainage. Definitive study of the abscess cavity should be deferred until the abscess has been effectively drained for several days.
2. Unsatisfactory clinical response may be due to partial drainage of septated collections or premature catheter removal.
3. An infected, obstructed calyceal diverticulum may be mistaken for a renal parenchymal abscess and continue to drain urine after the infection has cleared. Specific measures must then be directed toward dilating or occluding the neck of the diverticulum to prevent recurrence.

## PERCUTANEOUS DRAINAGE OF LYMPHOCELES

1. Lymphoceles that occur after renal transplantation or pelvic surgery can be drained percutaneously but usually recur if only simple drainage is performed.
2. Sclerotherapy of the lymphocele cavity appears to be more effective in preventing fluid reaccumulation than simple catheter drainage alone. Agents used for sclerotherapy include tetracycline, with povidone-iodine (Betadine), or absolute alcohol in combination with Betadine. However, the therapy requires several weeks of treatment and is making laparoscopic surgery to create a peritoneal window the procedure of choice.

## PERCUTANEOUS DRAINAGE OF URINOMAS

1. Urinomas are urine collections that result from extravasation of urine due to obstruction of the renal collecting system, surgery, or trauma and are often contained within a fibrous pseudocapsule.
2. Urinomas may cause secondary ureteral obstruction.
3. Large urinomas can be aspirated or drained in conjunction with management of the cause of the urine leak with PCN and ureteral stenting. However, not all urinomas require drainage because small (and occasionally large) urinomas will usually resorb spontaneously if the urinary obstruction is relieved.

## Renal Cyst Aspiration and Ablation

### INDICATIONS

Primary indication for this procedure is to decompress and/or obliterate a symptomatic benign simple renal cyst. Percutaneous ablation of a renal cyst is indicated if the lesion is producing pain, obstructive hydronephrosis, or segmental compression of portions of the collecting system with stasis of urine resulting in stone formation. Pain is the most common indication to perform renal cyst ablation.

### CONTRAINDICATIONS

1. An uncorrected bleeding diathesis
2. Aspiration and ablation of cysts in autosomal dominant polycystic kidney disease is rarely performed because of the difficulty in localizing a specific cyst or locule that may be causing the symptoms. Here again, the most common indication is flank pain.

### TECHNIQUE

1. Renal cysts are aspirated with a 20-gauge needle, using CT, or, most often, US guidance.
2. If the cyst is being punctured to ascertain whether it is responsible for the patient's flank or back pain, as much fluid as possible is aspirated from the lesion for a therapeutic trial. Ablation is deferred for a few weeks to see if the patient’s flank pain responds to the cyst decompression, and if it recurs when fluid reaccumulates within the cyst.
3. For cyst ablation, a small catheter or sheath is placed in the lesion, the majority of the cyst fluid is aspirated, and a sclerosing agent is then instilled into the cyst. The agent is left in for approximately a half hour and then aspirated before the catheter is removed.
4. Many sclerosing agents can obliterate renal cysts. Absolute alcohol is most often used because it appears to be the most consistent in its action.

### RESULTS

1. Most renal cysts reaccumulate after diagnostic aspiration, even if the cyst is drained completely.
2. The majority of renal cysts can be permanently obliterated, thereby relieving the symptoms that prompted the intervention.

### COMPLICATIONS

1. Improper needle placement may cause perinephric hemorrhage, inadvertent puncture of adjacent organs (e.g., lung, gastrointestinal tract), infection, arteriovenous fistula, and urinoma formation.
2. Extravasation of sclerosing agents into the perinephric tissues can cause fat necrosis, soft tissue fibrosis, or a febrile reaction.

## Urinary Tract Biopsy Techniques

1. Soft tissue and visceral lesions related to the urinary tract and suspicious nodes lesions can readily be sampled for cytologic or histologic analysis when necessary for patient management. Prostate needle biopsy is considered elsewhere in this book.
2. Biopsies can be obtained with needles percutaneously placed into lesions (to biopsy renal masses, retroperitoneal masses, or nodes). Biopsy of urothelial lesions can be performed through percutaneously placed catheters or through retrograde catheters placed with cystoscopic guidance.

### INDICATIONS

1. Evaluation of renal and adrenal masses in patients with a history of malignancy
2. A significant number, approximately 20%, of small renal masses may be benign but indistinguishable from renal cell cancer by imaging criteria. Interest is increasing in biopsying these masses for management decisions because the availability of immunohistochemistry often makes a definitive diagnosis possible on very small specimens.
3. Evaluation of urothelial irregularity or filling defects in patients with a past history of bladder or upper-tract urothelial cancer, or with hematuria

### CONTRAINDICATIONS

1. Contraindications to needle-aspiration biopsy include the following:
   a. Hemorrhagic diathesis
   b. Suspicion of an arteriovenous malformation in the area to be biopsied

2. There are no contraindications to transcatheter brush biopsy.

## TECHNIQUE

1. Needle biopsy
   a. Most percutaneous biopsies are guided by CT or US, some by MRI, with operator preference, lesion size and location, and machine availability determining the modality used for guidance.
   b. Biopsies performed with small (21- to 22-gauge), thin-walled needles yield samples for cytologic evaluation. Larger needles (14- to 20-gauge), often used in conjunction with automated, spring-loaded biopsy devices, yield specimens for histologic evaluation.
   c. Aspiration biopsies are obtained and evaluated immediately by a cytopathologist to ascertain the adequacy of tissue sampling. Additional biopsies are performed until diagnostic material is obtained.
   d. Large needles provide tissue cores of sufficient size for conventional histopathologic examination.
2. Transcatheter biopsy
   a. This approach is most frequently used to obtain a brush biopsy of a pyelocalyceal or ureteral lesion suspicious for transitional cell carcinoma on noninvasive imaging studies.
   b. An open-ended catheter is passed cytoscopically into the ureter or kidney. A guide wire on which a nylon brush is mounted is then passed through the catheter and the suspicious abnormality "brushed" under fluoroscopy. Exfoliated cells retrieved by the brush are subjected to cytologic analysis. A variety of brush configurations are available for approaching lesions through the collecting system and ureter. Other biopsy instruments, including forceps and snares, can be passed through larger catheters or sheaths inserted into the upper urinary tract.

## RESULTS

1. Transcatheter and percutaneous brush biopsies yield true-positive results in over 90% of cases. False-positive results are very infrequent.
2. Cytologic demonstration of malignant cells generally alters patient management by obviating the need for more invasive diagnostic techniques (including ureteroscopy), surgical biopsy, or staging procedures.

3. Negative findings do not exclude the presence of malignancy because they may represent sampling error. Therefore thin-needle aspiration or transcatheter brush biopsy is of value only when positive results are obtained.
4. Tissue-core biopsies analyzed histologically may have fewer false-negative results.

## COMPLICATIONS

1. Complications include the following:
   a. Blood vessel injury with bleeding, pseudoaneurysm, or arteriovenous fistula formation
   b. Peritonitis due to bowel leak
   c. Pneumothorax
   d. Seeding of the needle track with malignant cells.

      This may be more a theoretical than an actual risk. Only a handful of cases of spread of renal malignancy following aspiration biopsy has been reported. Nonetheless, because of the propensity for urothelial (but not parenchymal) tumors to spread along epithelial surfaces, suspected urothelial malignancies should not be biopsied percutaneously.
2. Brush biopsy is rarely associated with complications.
   a. Patient discomfort and hematuria related to catheter manipulation and vigorous "brushing" of friable lesions

      It is best to perform these biopsies with conscious sedation to keep the patient comfortable.
   b. Collecting system or ureteral perforation with catheters or guide wires can occur but are innocuous if adequate urinary drainage, usually with a retrograde ureteral catheter, is maintained for a day or two after the procedure.

## IMAGE-GUIDED ABLATION OF RENAL TUMORS

Percutaneous tumor ablation is becoming a viable option for patients with renal cell cancer in whom nephron-sparing surgery is contraindicated because of significant comorbidities. The role of percutaneous ablation therapy in patients without surgical contraindications is still unclear. The two techniques in current use are radiofrequency ablation (RFA) and cryotherapy. Although RFA was initially the most widely used technique, cryotherapy is increasingly preferred because its ability to visualize the zone of necrosis as the procedure is performed is an advantage. Cryoablation also can be used to treat larger tumors than with

RFA, and it is associated with fewer complications when treating central tumors near the collecting system.

## RADIOFREQUENCY ABLATION

Electrodes are placed percutaneously in the tumor with CT guidance, and a high-frequency alternating current is applied to heat the tumor to 50 degrees C, which coagulates the tissues. Tumors that can be successfully ablated are usually less than 5 cm in diameter and located in the periphery of the kidney. Centrally located tumors are more resistant to RFA than peripheral tumors because the large vessels in the renal hilus disperse the heat, resulting in incomplete ablation. Ablation of centrally located tumors is also associated with a higher risk of injury to the collecting system. Anteriorly located tumors are often in proximity to the colon, and special maneuvers are necessary to prevent thermal injury to the colon. Tumor ablation is assessed by lack of enhancement of the lesion on follow-up contrast-enhanced studies, whereas foci of enhancing tissue indicate the presence of viable tumor.

## CRYOABLATION

Cryoablation has been used with open surgery and percutaneously. Cell death is produced by producing extracellular and intracellular ice-crystal formation, and this "ice ball" can be visualized with imaging as the procedure is performed. Other techniques that are being investigated for renal tumor ablation include high-intensity focused ultrasound, microwave therapy, and renal ablation.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## Self-Assessment Questions

1. *What is the best way to evaluate a patient presenting with acute flank pain?*
2. *What is the role of imaging in a patient with suspected acute pyelonephritis?*
3. *How should a patient with mild renal insufficiency and suspected transitional cell carcinoma be managed?*
4. *How should a patient with a primary neoplasm, such as a lung cancer, and an adrenal lesion be managed?*
5. *What factors influence the management of a patient with urinary tract calculi?*

## Suggested Readings

1. Dunnick NR, Sandler CM, Amis ES: *Essentials of uroradiology*, ed 4, Baltimore, 2007, Lippincott Williams & Wilkins.
2. Levine MS, Ramchandani P, Rubesin SE: *Practical fluoroscopy of the GI and GU tracts*. New York, 2012, Cambridge University Press.
3. Morcos SK, Cohan RH, editors: *New techniques in uroradiology*. New York, 2006, Taylor & Francis.
4. Pollack HM, McClennan BL, editors: *Clinical urography*, ed 2, Philadelphia, 2000, Saunders.

## CHAPTER 3

# Lower Urinary Tract Infections in Women and Pyelonephritis

Philip M. Hanno, MD, MPH

## Lower Urinary Tract Infection

### DEFINITION

The urine is normally free of bacteria. *Bacteriuria* indicates the presence of bacteria in the urine. Bacteriuria can be symptomatic or asymptomatic. *Pyuria* is the presence of white blood cells in the urine and, when seen in conjunction with bacteriuria, is indicative of a true infection. *Asymptomatic bacteriuria* (ASB) is the isolation of bacteria from the urine in significant quantities consistent with infection, but without the local or systemic genitourinary signs or symptoms. The presence of ASB in the absence of symptoms or pyuria is often referred to as *colonization*. *Cystitis* refers to the symptoms of dysuria, urgency, frequency, and/or suprapubic pain. Infection (*bacterial cystitis*) is only one of many causes of this symptomatology, but one which is generally easy to prove or disprove with a simple urine culture.

### DIFFERENTIAL DIAGNOSIS

***Includes, but is not limited to:***

Vaginitis
Urethritis
Interstitial cystitis/bladder pain syndrome
Radiation cystitis
Bladder calculi
Overactive bladder
Bladder cancer

Other important definitions include:

1. Prophylactic antimicrobial therapy: Prevention of infection in a sterile urinary tract by administration of antimicrobial medications.
2. Suppressive antimicrobial therapy: Prevention of a clinically symptomatic infection in an asymptomatic patient whose urinary tract is colonized with bacteria.
3. Nosocomial urinary tract infection (UTI): Those that occur in hospitalized or institutionalized patients.

## CLASSIFICATION SCHEMA

Urinary tract infections (UTIs) can be classified as to their *site of origin*. Cystitis refers to the nonspecific clinical syndrome of dysuria, urinary frequency, urgency, and suprapubic pressure. Fever, chills, and flank pain can indicate the presence of pyelonephritis, an interstitial inflammation caused by bacterial infection of the renal parenchyma. **Surprisingly, based on symptoms, it can be remarkably difficult to differentiate infection involving the upper tracts from bacteriuria confined to the bladder.** Many patients with pure lower tract symptoms will have positive cultures of renal pelvic and ureteral urine if catheterization of the upper tracts is performed. Conversely, some patients with flank pain will be found to have only cystitis on differential urine cultures. Fortunately, from a practical standpoint, it is not generally an important distinction, and localizing the site of infection in clinically uncomplicated infections is unnecessary.

UTIs can also be classified in terms of the *anatomic or functional status of the urinary tract* and the overall health of the patient. An uncomplicated infection indicates it is occurring in an otherwise normal urinary tract in a healthy individual. A complicated infection is one occurring in a functionally or structurally abnormal urinary tract, in a host with a compromised immune system, or an infection with bacteria of increased virulence or antimicrobial resistance (i.e., nosocomial UTI).

**Perhaps the most useful classification of UTI for the primary care provider is that devised by Tom Stamey of Stanford University and based on the relationship of UTI episodes with each other.** *First infections* refer to isolated or remotely occurring bacterial cystitis. These are the most common infections in women, occurring in 25% to 30% of women between the ages of 30 and 40 years. *Unresolved bacteriuria* occurs when the urine cannot be sterilized despite antibiotic treatment. Common causes include preexisting or acquired bacterial resistance, inadequate coverage of a second organism, rapid reinfection with a new organism during therapy, azotemia preventing access of the antibiotic to the urinary tract, and noncompliance with treatment. *Recurrent infection* is an infection diagnosed after successful treatment of an antecedent infection. This category represents 95% of recurrent UTIs in women. The other 5% may be caused by *bacterial persistence*. In this category, sterilization of the urine is short-lived, and within weeks, a relapse with the identical organism occurs. Such infections indicate a site of persistent infection within the urinary tract that could be a manifestation of an infected staghorn calculus, enterovesical fistula, or infected anatomic anomaly such as a diverticulum in the urinary tract.

## EPIDEMIOLOGY

UTIs are considered to be the most common bacterial infection. They are generally associated with minimal morbidity except among specific subpopulations. Eleven percent of women report having had a UTI during any given year, and more than half of all women have had at least one UTI in their lifetime. One in three women have a UTI before the age of 24 years. This contrasts with men, in whom infection is uncommon until after the age of 50 when the problem of an enlarged prostate and outlet obstruction may occur. Between 3.5 and 7 million office visits a year are the result of UTI, and direct costs exceed $1.6 billion. It is difficult to assess the true incidence of UTI because urine cultures are not often done in the outpatient setting, and symptoms are variable.

Catheter-associated UTI is the most common nosocomial infection. The risk of bacterial colonization increases with the duration of catheterization, approaching 100% at 30 days. UTI accounts for 25% of infections in the noninstitutionalized elderly. Thankfully, for such a common problem, UTI in the nonobstructed, nonpregnant female adult acts as a benign illness with no long-term sequelae. This is not true in other populations as noted in Box 3-1.

BOX 3-1 **Subpopulations at Increased Risk from UTI**

1. Infants
2. Pregnant women
3. Elderly
4. Spinal cord injury
5. Indwelling catheters
6. Diabetes
7. Multiple sclerosis
8. Acquired immunodeficiency disease
9. Underlying urologic abnormalities

Symptomatic UTI is especially common among sexually active women. Modifiable behavioral risk factors include the use of a diaphragm and spermicides for contraception and frequency of sexual intercourse among premenopausal women. Estrogen deficiency is another risk factor, as is antimicrobial use itself. In women with a first UTI, 24% will have a second episode within 6 months, and up to half of women will have a second infection within a year. The risk of recurrent uncomplicated bacterial cystitis remains unchanged whether the initial episode is left untreated to clear spontaneously, or treated with short-term, long-term, or prophylactic antimicrobial therapy. Symptomatic episodes in the healthy population are more of a nuisance than a threat to health. **No association between recurrent infections and renal scarring, hypertension, or renal failure has been established in patients with uncomplicated, simple recurrent UTI.**

ASB is present in 3% of women in their early 20s, rising from 1% with the onset of intercourse in the late teenage years. It increases 1% per decade. The incidence of ASB in the pregnant population is similar to the nonpregnant population, but the implications are more concerning. The risk during pregnancy for pyelonephritis is increased substantially in those harboring bacteria in the urinary tract, especially during the end of the second and beginning of the third trimester. Studies suggest a 20% to 40% incidence of pyelonephritis if ASB is untreated in this population.

Diabetes increases the risk of UTI and bacteriuria among female but not male patients. UTIs in ambulatory patients with diabetes are considered complicated, with a heightened risk for pyelonephritis and severe complications if left untreated. UTI is more common in the multiple sclerosis population and can herald acute exacerbations and progression of the disease. Approximately 11% to 25% of elderly, noncatheterized patients can develop transient ASB, and persistent colonization in the elderly may affect up to 50% of geriatric women and be extremely difficult to eradicate.

## PATHOPHYSIOLOGY

The paradigm of uncomplicated UTIs is that bacterial virulence appears to be crucial for overcoming normal host defenses. With complicated UTI, the paradigm is reversed, in that bacterial virulence is much less important, and host factors tend to be critical.

The bacteria responsible for UTIs are normally present in the bowel. *Escherichia coli* is the most common, accounting for 85% of community-acquired infections and up to 50% of nosocomial infections. New research from Kylie Mansfield in Wollongong, Australia, suggests that the specific serotype of the lipopolysaccharide of the *E. coli* cell wall may determine whether or not ATP is released from the urothelium when it is stretched, resulting in either clinical cystitis or just asymptomatic colonization. Other common organisms include *Proteus sp*., *Klebsiella sp., Enterococcus faecalis,* and *Staphylococcus saprophyticus*. The female urethra is short, and bacteria generally enter the bladder in an ascending fashion.

Vaginal mucosal introital colonization generally precedes infection and is determined by bacterial adherence, the receptive characteristics of the epithelial surface, and the fluid that bathes both surfaces. Estrogens and pH affect attachment and colonization of the vaginal mucosa. Host defense mechanisms include the antiadherence properties of the vaginal and bladder mucosa, the hydrokinetic clearance of bacteria through voiding, and changes in urine pH and composition that may inhibit bacterial growth. Women with recurrent UTIs demonstrate increased adherence of bacteria in vitro to uroepithelial cells when compared to findings in women who have never had an infection. Studies suggest that this may be genetically determined.

Kunin has found strong statistical evidence that the female urethra has a powerful antimicrobial defense mechanism that appears to differ in women with and without recurrent UTI. The female urethra is lined by cells identical to those of the vagina that respond readily to estrogens. The normally functioning urethra may help to protect the bladder from cystitis through the shedding of uropathogens bound to exfoliating urethral cells; trapping of bacteria by mucus secreted by the paraurethral glands; intermittent washout by urine, local production of immunoglobulins, cytokines and defensins; and mobilization of leukocytes.

It is generally believed that some failure with the host defense mechanism allows for colonization of the introitus and vaginal mucosa in women subject to recurrent bacterial infection from reinfection outside the urinary tract. While colonized, these women can experience repeated infections for 6-12 months or more, each readily treated with antibiotics, but recurring within weeks or months. This introital colonization is of limited duration, and may resolve after 1 or 2 years and leave the patient asymptomatic until the next episode of colonization when subsequent bouts of infection begin.

Recent research by Gregory Anderson, Scott Hultgren, and colleagues at Washington University in St. Louis has demonstrated a new and possibly important mechanism by which *E. coli* can seed the bladder urine in the absence of introital colonization. They have shown in animal models that bacteria can subvert the innate host defense responses by invasion into the bladder superficial cells. Intracellular bacteria mature into biofilms, creating podlike bulges on the bladder surface. Pods contain bacteria encased in a polysaccharide-rich matrix surrounded by a protective shell of uroplakin. This can provide an internal reservoir of bacteria capable of causing clinical bacterial cystitis.

*S. saprophyticus* and enterobacterial species adhere to uroepithelial cells through different adhesive mechanisms than *E. coli*. After attachment, *Proteus* spp., *K. pneumoniae*, and *S. saprophyticus* each produce urease, which catalyzes the hydrolysis of urea in urine and causes the release of ammonia and $CO_2$. This elevates the urinary pH and can lead to the formation of bladder or kidney stones.

**Risk factors for UTI include sexual intercourse, use of a diaphragm or cervical cap, and spermicidal jelly, which can alter the normal vaginal flora.** The ABO-blood group nonsecretor phenotype is at increased risk for vaginal colonization with uropathogenic bacteria. Urologic instrumentation, diabetes, and age-related changes in the elderly patient are also risk factors. Low estrogen levels allow vaginal pH to rise, resulting in a higher likelihood of vaginal colonization with *E. coli*. The use of oral contraceptive agents is unrelated. Personal hygiene habits are not generally related to recurrent UTI, and it is wise to assure patients that this represents a biologic phenomenon rather than a result of poor cleanliness.

## DIFFERENTIAL DIAGNOSIS: SIGNS AND SYMPTOMS, DIAGNOSTIC STUDIES

The history is a critical component in the diagnosis of UTI. The diagnosis is often made on history alone. The probability of bacterial cystitis in a woman with dysuria, urinary frequency, or gross hematuria is about 50% in the primary care setting. Urethritis and vaginitis can also cause acute dysuria in women. Cystitis is usually caused by enteric gram-negative bacilli or *S. saprophyticus*. Urethritis is caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or herpes simplex virus. Vaginitis is caused by candidal species or *Trichomonas vaginalis*. Pyuria is rare in vaginitis but common in urethritis and cystitis. A positive urine culture is usually present in bacterial cystitis. Symptoms of cystitis are usually severe and more acute than those in urethritis, which can be mild, gradual in onset, and include vaginal discharge.

Symptoms suggesting vaginitis such as vaginal irritation or discharge reduce the likelihood of a diagnosis of cystitis by 20%. Dysuria and frequency in the absence of vaginal discharge raise the probability of acute UTI to 90%. If the woman has a history of culture-documented bacterial cystitis and experiences similar symptoms, the chance of a true infection approaches 90%.

Urologic investigation is not routinely indicated in women with isolated episodes of acute urinary frequency, dysuria, and urgency suggestive of lower UTI. Diagnosis is often empiric; however, a urinalysis and/or culture can provide helpful documentation of the true diagnosis and responsible organism (Table 3-1). Examination of urine sediment after centrifugation will show microscopic bacteriuria in more than 90% of infections with $10^5$

TABLE 3-1 **Diagnosis of UTI**

| Test | Sensitivity | Specificity |
|---|---|---|
| Pyuria | 95% | 71% |
| Bacteriuria | 40%-70% | 85%-95% |
| Dipstick nitrite + or leukocyte esterace + | 75% | 82% |
| Midstream clean-catch pure culture | | |
| >100,000 bacteria/mL | 50% | 80% |
| >1,000 bacteria/mL | 70%-90% | High if dysuria |

A positive dipstick (nitrite or leukocyte esterase positive) indicates that the likelihood of infection is 25% higher than the pretest probability. A negative test indicates that it is 25% lower. A positive dipstick in the setting of consistent symptoms suggests treatment can be instituted without urine culture, provided there is an absence of factors associated with upper tract or complicated infection. A negative dipstick does not rule out infection when the pretest likelihood is high, and a urine culture in necessary in this situation. Culture is also critical in patients who do not respond to standard or initial therapy for UTI.

*(Adapted from Fihn SD: Acute uncomplicated urinary tract infection in women,* NEJM*, 349:259-266, 2003.)*

colony forming units (CFU)/mL. Pyuria will be seen in 80% to 95% of infections, and microhematuria in about 50%. False-positive urinalyses are commonly caused by normal vaginal flora appearing to be gram-negative bacteria on urinalysis, and pyuria that can be the result of a variety of other inflammatory conditions of the urinary tract. Alternatively, a false-negative urinalysis is commonly the result of urinary dilution from a high fluid intake in the symptomatic patient and frequent voiding, which prevents the bacteria in the bladder from multiplying to the high counts commonly associated with UTI. A recent meta-analysis suggests that urine dipstick findings of nitrituria increase the odds of a positive culture by a factor of 11 whereas a dipstick finding of leukocyte esterase increases the likelihood of a culture documented infection by a factor of over 3.

If a urine culture is performed, it should be a carefully collected, midstream specimen to decrease the likelihood of any vaginal contamination. Approximately one third of women with acute symptomatic cystitis caused by *E. coli*, *S. saprophyticus*, or *Proteus* sp. have colony counts of midstream urine specimens ranging from $10^2$ to $10^4$ CFU/mL. Thus a pure culture in the presence of symptoms must be considered significant, regardless of colony count.

Clues in the history that may suggest an increased risk of complicated UTI include childhood bladder or kidney infections, previous urologic surgery or instrumentation, an unusual causative organism, urolithiasis, or the presence of diabetes. If hematuria is noted, the physician is obligated to be sure that it is no longer present after treatment of infection. If it persists, a urologic imaging study and cystoscopy are necessary to rule out other urologic pathology. If a complicated UTI is suspected by history, a similar evaluation may be required.

Imaging studies should be considered in the following situations:

1. Women with febrile infections
2. Men
3. If urinary tract obstruction is suspected, history of:
    a. Calculi
    b. Ureteral tumor
    c. Ureteral stricture
    d. Congenital ureteropelvic junction obstruction
    e. Previous urologic surgery or instrumentation
    f. Diabetes
4. Persistent symptoms despite several days of appropriate antibiotic therapy
5. Rapid recurrence of infection after apparently successful treatment

Ultrasonography is an excellent initial screening test when imaging is indicated. It is noninvasive, does not cause radiation exposure, does not risk contrast reaction, and is generally readily available. It can identify stones, obstruction of the upper tracts, abscess, and many congenital abnormalities. CT and MRI provide the best anatomic data on the site, cause and extent of infection. **The key point to remember is that in the vast majority of symptomatic lower UTIs, imaging does not have a role to play in diagnosis or treatment.**

## THERAPY: GENERAL CONSIDERATIONS

The management of UTIs is complicated by the increasing prevalence of antibiotic-resistant strains of *E. coli* and other common uropathogens. In the past, antibiotic resistance had been a problem only in the management of complicated nosocomial urinary infections. This resistance has now spread to uncomplicated community-acquired UTIs. Local antibiotic resistance rates are critical if one is to make an informed decision on empiric therapy. In many countries the resistance of *E. coli* for trimethoprim has already exceeded the threshold for empiric therapy of 20%, and resistance for fluoroquinolones is also rising, approaching 30% in urologic populations. Ampicillin resistance rates are among the highest, and ampicillin is not recommended for empiric therapy. Of course, once cultures are obtained, and/or if therapy is initiated after sensitivity data is available, the least expensive and most limited spectrum antibiotic with appropriate sensitivities would be preferred. A superb review by Naber et al. (2011) is among the suggested references below.

Resistance development tends to follow usage patterns, and, as of 2006, quinolones have surpassed sulfas as the most common class of antibiotics prescribed for isolated outpatient UTI in women. This growth of the use of a potentially lifesaving, broad spectrum antibiotic for what is, in most patients, a "symptomatic nuisance," raises concerns about increases in resistance to this important class of antimicrobials in the future. The question arises as to whether it is better to potentially undertreat 5% to 20% of patients with recurrent UTI from reinfection, and subsequently change antibiotics after 2 or 3 days if there is no clinical response, than to overtreat the vast majority with a quinolone. This author would answer yes in the majority of patients with uncomplicated, recurrent UTI from reinfection from a site outside the urinary tract.

Resistance patterns tend to be very local. Therefore it is helpful to know the patterns of microbial resistance in your city and even in your hospital and surrounding outpatient clinics. Because urine levels of antibiotic are much more important than serum levels in determining efficacy for treating UTI, many antibiotics that appear to be poor choices based on sensitivity data relating to serum levels may eradicate UTI when administered because of high urinary excretion rates.

## UNCOMPLICATED ISOLATED CYSTITIS

Treatment of isolated cystitis is often empirical and not based on culture data. A drug should be chosen based on the following criteria:

1. The relative likelihood that it will be active against enteric bacteria that commonly produce UTIs.
2. Ability to achieve high concentrations in the urine.

3. Tendency not to alter the bowel or vaginal flora or to select for resistant bacteria.
4. Limited toxicity
5. Availability at reasonable cost to the patient

Because organisms causing isolated UTI in the community are generally pansensitive to antibiotics, cost and convenience are major factors in drug selection.

Urine levels of antimicrobial rather than serum levels are important for efficacy in eliminating bacteria. Care must be taken in interpreting antibiotic susceptibility tests because they are often based on serum levels of drug. In the past, physicians prescribed treatment for 5-10 days. **It is now apparent that 3 days of antibiotic will suffice to clear the vast majority of uncomplicated UTIs.** Single-dose therapy is slightly less efficacious, and symptoms can persist even after the urine has become sterile, leading to patient requests for more antibiotic.

An inexpensive, generic, narrower spectrum antibiotic is often a good choice in this setting. One can always move to a more expensive, broad spectrum antibiotic if symptoms are not relieved in 2 or 3 days, and a subsequent culture indicates a resistant organism. But in the vast majority of cases, the choice of trimethoprim-sulfamethoxazole (TMP-SMX) or nitrofurantoin will prove to be adequate to treat the infection, will be much less expensive for the patient, and will result in less chance of community bacteria acquiring resistance to powerful alternative antibiotics that can be lifesaving when used in appropriate situations.

## UNRESOLVED BACTERIURIA

Persistent symptoms following treatment for UTI necessitate urine culture and sensitivity testing. Choice of antibiotic will depend on the results obtained, and a 7-10 day course would be reasonable. Repeat culture and bacterial identification following treatment for unresolved bacteriuria is important in order to later differentiate the problem from recurrent infection from a site within the urinary tract.

## RECURRENT BACTERIAL CYSTITIS

A detailed culture history is critical in differentiating reinfection from a site outside the urinary tract as the cause of recurrent cystitis from reinfection from a site of bacterial persistence within the urinary tract. The former accounts for over 95% of cases of recurrent UTI, but the latter is important because a full urologic evaluation is mandatory. Bacterial identification is essential; recurrent infections that occur after successful antimicrobial eradication (negative culture) and that are subsequently caused by varying strains of *Enterobacteriaceae* are pathognomonic for reinfection. The only confounding factor that might cause a similar scenario is reinfection from an enterovesical fistula with different organisms. In this unusual case, often the urine can never be sterilized, and infections may be with multiple organisms, thus leading to suspicion of a fistula.

This author tends to be aggressive in evaluating patients with long histories of recurrent UTIs in order not to miss a treatable etiology. A renal and bladder ultrasound will demonstrate normal anatomy, absence of infection stones, and low bladder urinary residual volume, and serves as a good initial screening test in this group of patients. Cystoscopy can be reserved for those patients where there is suspicion of a fistula, infected suture, or voiding dysfunction that may be related to functional or anatomic obstruction.

Once it is clear that the patient's problem represents recurrent cystitis from reinfection from a site outside the urinary tract, usually gram-negative introital colonization, one can discuss treatment strategies with the patient. The patient should be reassured that the problem is largely one of controlling the symptoms, and is not a threat to her urologic health. It is a treatable nuisance that most patients can manage on their own without numerous visits to physicians' offices.

Cranberry has been used as a folk remedy to prevent recurrent UTI for many years. In the 1920s it was thought the mechanism was urinary acidification. Sixty years later, cranberry was found to interfere with the attachment of bacteria to uroepithelial cells. A recent meta-analysis by Wang et al. (2012) (see suggested references) indicates that cranberry-containing products are associated with a protective effect against UTIs. However, the trials tend to be very heterogeneous, and, in the majority of cases, other treatment strategies need to be employed.

Years ago, many patients were treated with long-term, low-dose antibiotic therapy. This might have been 50 mg nitrofurantoin every evening or a half tablet of TMP-SMX every other night for 6 months. At that point, treatment would stop in the hope that the introital colonization with uropathogenic gram-negative organisms had resolved, which tends to happen over time. Two or three episodes of UTI over the next 6 months would trigger another course of prophylaxis.

In an effort to decrease overall antibiotic usage, equally effective strategies have emerged. "Self-start" therapy relies on the patient to make the clinical diagnosis of UTI, which is not difficult for these patients. It presumes that symptom episodes in the past have been confirmed to be infectious by culture. Patients are given a prescription for an appropriate urinary antibiotic (nitrofurantoins, TMP-SMX, cephalexin), which they take for 2 or 3 days at the first symptom of infection. While some physicians encourage dip-slide culture before and after medication, this author believes that if the symptoms respond quickly to a short course of antibiotic, culture is not necessary. Only if the symptoms do not respond or reoccur within a few days, is a visit to the health care provider for appropriate culture and sensitivity testing required. Certainly, systemic symptoms, such as fever and flank pain, or the presence of gross hematuria should trigger a visit to the physician. With appropriate patient education, self-treatment seems to work very well in properly diagnosed recurrent UTI from reinfection. Antibiotic therapy for 3 days is similar to prolonged therapy in achieving symptomatic cure for cystitis, though prolonged therapy is marginally more effective in obtaining bacteriological cure.

Single-dose therapy is another option in this setting. Although this might clear the bacteria from the urinary tract, symptoms often persist for 48 hours, and the patient is left unsure as to whether more antibiotic or a different antibiotic is required. If infections seem to be exclusively related to intercourse, and frequency of intercourse is not too high, one can consider a prophylactic antibiotic just before sexual activity to prevent infection. Those having sex four or more times weekly might be better off treating only symptomatic infections with short-term courses of antibiotics, thus limiting overall use of antibiotic.

## CHOICE OF ANTIBIOTIC

A variety of excellent, inexpensive, first-line antimicrobials can be considered for the treatment of uncomplicated lower UTIs in women. **Nitrofurantoin, while not effective against** *Pseudomonas*

**and *Proteus* species, does cover the vast majority of pathogens encountered, and development of resistance over the last 30 years has not been a problem.** It has high urine levels, a short half-life in the blood, and minimal effect on resident fecal and vaginal flora. It seems ideal for short-term use. It should not be administered to patients with known G6PD deficiency. A rare pulmonary toxicity limits its use for long-term, low-dose continuous prophylaxis.

Trimethoprim with or without sulfamethoxazole is another widely used and very effective treatment for UTI. While resistance to TMP-SMX has increased in the last decade, in many locales this is not a problem, and treatment can be changed if symptoms prove unresponsive or cultures show bacterial resistance. Alone or in combination, these drugs will not eradicate *Enterococcus* and *Pseudomonas* species. They are inexpensive and can clear the vaginal flora of gram-negative uropathogens, although the clinical significance of this is questionable. Skin rashes and gastrointestinal (GI) side effects prove the main drawbacks.

Cephalosporins, as a group, have poor activity against *Enterococcus*. First-generation drugs are reasonable to treat uncomplicated UTI, but the second- and third-generation members of this group should be reserved for culture-documented infections requiring their broader coverage. **Ampicillin and amoxicillin, traditionally regarded as inexpensive first-line therapy, have generally fallen out of favor due to their interference with the fecal flora and the resultant emergence of resistant strains such that these drugs are now ineffective against as many as 30% of common urinary isolates.**

Although the fluoroquinolones have a very broad spectrum of activity against most urinary pathogens, including *Pseudomonas aeruginosa*, their routine use for treatment of uncomplicated UTI is to be avoided. Gram-positive activity is limited, and efficacy against *Enterococcus* is poor. These are expensive, powerful oral agents. The fear that overuse may lead to the development of resistance and the fact that, for most uncomplicated UTIs, less expensive drugs are just as effective has tended to limit their use. Alarming reports of community-acquired UTIs caused by fluoroquinolones-resistant *E. coli* strains in some parts of the world suggest that we will see an evolution of resistance to these agents just as we have with sulfonamides, ampicillin, oral cephalosporins, and TMP-SMX unless a much more aggressive approach to the control of antimicrobial resistance in taken. The fluoroquinolones remain a valuable class of antibiotic, best restricted to complicated UTIs, pseudomonal infections, or treatment of resistant organisms.

Fosfomycin, a naturally occurring antibiotic originally described under the name *phosphomycin* in 1969, is commonly used for UTI in many parts of the world. A single 3-gram dose of fosfomycin trometamol has been recommended for the empiric therapy of uncomplicated cystitis in women. The low level of *E. coli* resistance does not seem to be jeopardized by its high consumption in some areas. In countries where it has been used for many years, about 3% of bacterial pathogens are resistant to fosfomycin, and this percentage has been stable for several years. It gives very high and sustained urinary concentrations that rapidly kill bacteria reducing the opportunity for mutant selection.

**Long-term use of antibiotics can lead to resistance, so methenamine salts (methenamine or hexamine hippurate) are often used for chronic therapy.** These are termed *urinary antiseptics*. They are absorbed from the gut and pass into the urine where they release the chemical formaldehyde if the urine is acidic. To assure urinary acidity, they are administered (1 gram twice daily) with vitamin C. Formaldehyde causes the breakdown of proteins essential to the bacteria, which ultimately results in their death. The Cochrane Review found that not enough evidence exists about whether methenamine hippurate can prevent UTIs, although it might work and more research is needed. This is unlikely to occur because the methenamine salts are old generic drugs that no company is likely to invest in to study. Adverse effects are minor and uncommon. This author likes to use methanamine hippurate in patients with recurrent UTI who harbor residual urine which allows the medication to release formaldehyde and keep bladder urine colony counts low, thus decreasing incidence of symptomatic infection. It is an ideal drug for patients on intermittent catheterization who present with recurrent symptomatic UTI. It is best to sterilize the urine with an appropriate antibiotic before initiating therapy.

## SPECIAL SITUATIONS

Indwelling urinary catheters are used frequently in older populations. For either short- or long-term catheters, the infection rate is about 5% per day. During the initial 4 days of catheterization, concomitant antimicrobial therapy is associated with a decreased rate of infection. After 4 days, the infection rate is similar, whether or not antimicrobials are continued, but more resistant organisms are isolated from patients receiving antimicrobials. UTI follows formation of a biofilm on both the internal and external catheter surface. The biofilm is protective against antibacterials and also against the host immune response. **Antimicrobial treatment of asymptomatic catheter-acquired infection** (colonization) **should be discouraged because treatment in the presence of an indwelling catheter is unlikely to sterilize the urinary tract and acts to promote emergence of more resistant organisms, complicating management when subsequent symptomatic infection occurs.** Treatment should be reserved for symptomatic infections only.

The prevalence of bacteriuria in the elderly patient is surprisingly high. Up to 20% of women and 10% of men older than 65 years have bacteriuria. The figures are even higher for nursing home residents. The need for treatment of ASB in the elderly is controversial. It is not uncommon for courses of antibiotics to be unsuccessful in long-term management of bacteriuria in this group of patients. Studies suggest that noncatheterized male and female residents with bacteriuria living in nursing homes have no higher frequency of courses of antimicrobial treatment, infections, or hospitalizations than those without persistent bacteriuria. As a result, screening for ASB in the elderly should be limited to those undergoing invasive urological procedures and surgical procedures with implant material. Pyuria accompanying ASB is not an indication for antimicrobial treatment. In patients about to undergo surgery for implantation of foreign material, or any urologic surgery, the ASB should be treated and the urine sterilized if possible. Clearly, symptomatic UTIs in the elderly patient should be appropriately treated. In addition, it would seem prudent to treat any bacteriuria due to urea-splitting bacteria such as *Proteus mirabilis* to prevent stone formation. **Otherwise, the routine treatment of ASB in the elderly appears unjustified and is often ineffective.**

Pregnancy merits particular attention with regard to screening for bacteriuria and treatment of UTI. The prevalence of bacteriuria identified by screening is no higher in pregnant females than nonpregnant females of the same age. However, pregnancy results in physiologic changes that have important implications with regard to ASB and progression of infection. With pregnancy comes an increase in renal size, augmented renal function, hydroureteronephrosis, and anterosuperior displacement of the bladder. The frequency of acute pyelonephritis in pregnant women is significantly higher that in their nonpregnant counterparts. Studies suggest a 20% to 40% incidence of pyelonephritis if ASB is untreated in this population. In addition, bacterial pyelonephritis in pregnancy has been associated with infant prematurity and perinatal mortality. These factors make it prudent to screen for ASB in pregnancy, treat it aggressively, and obtain follow-up cultures. An initial negative screening urine culture need not be repeated because these patients are unlikely to develop bacteriuria later in pregnancy.

## Pyelonephritis

Infection of the upper urinary tract including the renal pelvis and kidney parenchyma is referred to as pyelonephritis. Acute pyelonephritis is characterized by acute suppuration accompanied by fever, flank pain, bacteriuria, and pyuria. Repeated attacks of acute pyelonephritis may result in chronic pyelonephritis, characterized by progressive renal scarring that can be asymmetric and involve both the cortex and pelvicalyceal system.

Several potential routes of upper tract infection are:

1. Ascending: Bacteria that reach the renal pelvis gain entry through the collecting ducts at the papillary tips and make their ascent through the collecting tubules. The presence of reflux of urine from the bladder or increased intrapelvic pressures from lower tract obstruction can facilitate upper tract infection, especially in the presence of intrarenal reflux.
2. Hematogenous: This is uncommon but can be a result of *staphylococcus aureus* septicemia or *Candida* in the blood stream.
3. Lymphatic: This is a very unusual form of extension to the renal parenchyma from an intraperitoneal infectious process (i.e. abscess).

## CLINICAL PRESENTATION

**The classic clinical scenario is the acute onset of fever, chills, and flank pain in a patient with obviously infected urine on urinalysis, subsequently proven on urine culture.** One must keep in mind that some patients with flank pain and UTI do not have upper tract infection and that patients can have pyelonephritis in the absence of local or systemic symptoms. A high index of suspicion is required in a patient with one of the known risk factors for pyelonephritis (Box 3-2).

Additional symptoms of acute pyelonephritis may include systemic malaise, nausea, and vomiting. Lower tract symptoms including dysuria and urinary frequency are commonly present. Pyelonephritis can result in sepsis, hypotension, and death, especially in the scenario of infection behind an unrecognized upper tract obstruction.

On physical examination, flank tenderness may be a prominent finding. An infected urine with the presence of large amounts of granular or leukocyte casts in the sediment is also suggestive of the diagnosis. *E. coli* possesses special virulence factors and accounts for 80% of cases of acute pyelonephritis. *Pseudomonas, Serratia, Enterobacter*, and *Citrobacter* are sometimes identified as causative microorganisms in complex cases with a history of urinary tract instrumentation, nosocomial infection, indwelling catheters, and/or ureteral stents.

Suspect *Proteus* or *Klebsiella* in patients with stone disease. *Proteus mirabilis* and some strains of *Klebsiella* contain the enzyme urease, which is capable of splitting urea with the production of ammonia and an alkaline environment. The latter

BOX 3-2 **Potential Risk Factors for Pyelonephritis**

1. Vesicoureteral reflux
2. Obstruction of the urinary tract (congenital ureteropelvic junction obstruction, stone disease, pregnancy)
3. Genitourinary tract instrumentation
4. Diabetes mellitus
5. Voiding dysfunction
6. Age (renal scarring rarely begins in adulthood but is generally related to intrarenal reflux in children)
7. Female gender

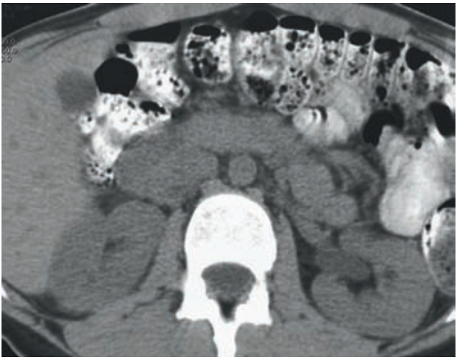

FIGURE 3-1 Acute pyelonephritis in 26-year-old female. Precontrast CT does not help in making diagnosis. (Courtesy of Parvi Ramchandani, MD).

is favorable for precipitation of the salt struvite (magnesium ammonium phosphate). Struvite may form branched calculi that harbor bacteria in the interstices of the stone. These so-called *staghorn calculi* can cause chronic renal infection, abscess, or chronic lower tract infection. The infection is difficult to cure unless the stone itself is removed.

The intravenous urogram may be normal or can show renal enlargement secondary to edema. Focal enlargement must be distinguished from a renal mass or abscess. Inflammation may cause a diminished nephrogram or delayed appearance of the pyelogram on the affected side. One of the most important aspects of any imaging study is to rule out the presence of urolithiasis and/or obstruction, which can lead to a life-threatening situation if not appreciated and relieved. Ultrasound can demonstrate many of the above findings and help to rule out an obstructive process. CT is also useful in some cases, and may show patchy decreased enhancement suggesting focal renal involvement (Figures 3-1 and 3-2).

## COMPLICATIONS

1. **Xanthogranulomatous pyelonephritis (XGP)** is an unusual, often severe, chronic renal infection that destroys the kidney. It is generally unilateral, associated with obstructing calculi, and results in an enlarged, nonfunctioning kidney that must be differentiated from malignancy. Perirenal fat may be

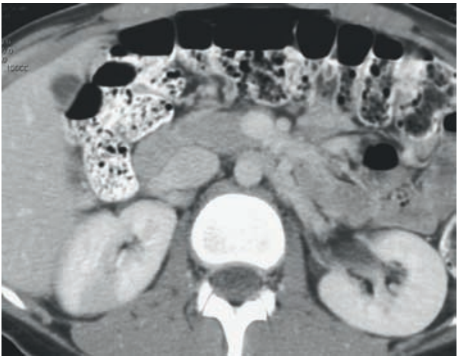

FIGURE 3-2 Postcontrast CT shows shows patchy decreased enhancement in right kidney. (Courtesy of Parvi Ramchandani, MD).

involved with adjacent subcapsular inflammatory response. *Proteus* and *E. coli* are the primary microbes responsible for initiating the inflammatory process. Pathologically, the kidneys consist of yellow-white nodules, pyonephrosis, and hemorrhage. Granulomatous inflammation with lipid-laden macrophages known as *xanthoma cells* is seen histologically. Suspect XGP in the patient with persistent bacteriuria accompanied by flank pain, fever, and chills in the presence of an enlarged, nonfunctioning kidney with a stone or solid mass lesion. CT and ultrasound aid in diagnosis. Treatment is generally nephrectomy, removing the entire inflammatory mass.

2. **Chronic pyelonephritis** is rare in the absence of underlying functional or structural abnormalities of the urinary tract. The symptoms are those of the chronic renal failure it produces, and a history of recurrent acute pyelonephritis may be elicited. Urine cultures may be negative. A localized scar over a deformed calyx is a classic presentation on imaging studies. Pathologically, the kidneys are often diffusely contracted, scarred, and pitted. Histologically, periglomerular fibrosis is common in conjunction with atrophied tubules.
3. **Renal insufficiency** is a rare complication of acute pyelonephritis.
4. **Hypertension** is noted in over 50% of patients with chronic pyelonephritis. This may be due to fibrosis of the

renal parenchyma with resulting ischemia and secondary activation of the renin-angiotensin system. Although hypertension can accelerate progressive renal failure, the fact that nephrectomy cures hypertension in selected patients suggests that the reverse is also true.

5. **Renal abscess,** a collection of purulent material confined to the renal parenchyma, may follow insufficient treatment of focal bacterial nephritis (lobar nephronia). Diagnosis is with CT and ultrasound. Needle aspiration and drainage of the abscess and prolonged antibiotic treatment often preclude the need for surgical drainage.
6. **Infected hydronephrosis** denotes the bacterial infection of a hydronephrotic kidney. When associated with suppurative destruction of renal parenchyma, the term *pyonephrosis* is used. Ultrasound and CT can usually make the diagnosis, and emergent drainage is required, usually by ureteral catheter or percutaneous catheter placement, until definitive relief of the obstruction is attempted.
7. **Perinephric abscess** can result from rupture of a cortical abscess or hematogenous seeding from another infected site. The primary treatment is drainage.
8. **Emphysematous pyelonephritis** is an acute necrotizing parenchymal and perirenal infection caused by gas-forming uropathogens. Diabetic patients are at increased risk. Complicating factors can include urinary tract obstruction secondary to calculi or sloughed necrotic papillae. Women are affected more commonly than men. Fever, vomiting, and flank pain constitute the classic triad of symptoms. The diagnosis is established by the finding on plain x-ray, CT, or ultrasound of intrarenal parenchymal gas. The disease can be fatal, and aggressive percutaneous renal and perirenal drainage or immediate nephrectomy, in combination with appropriate antibiotics, is critical. Most cases are associated with *E. coli,* though *Proteus, Klebsiella,* and *Candida albicans* can be responsible pathogens.

## MANAGEMENT (FIGURE 3-3)

Acute pyelonephritis can be managed on an outpatient basis with oral antibiotics in the patient who is not septic and does not suffer from nausea and vomiting. A fluroquinolone is a good choice

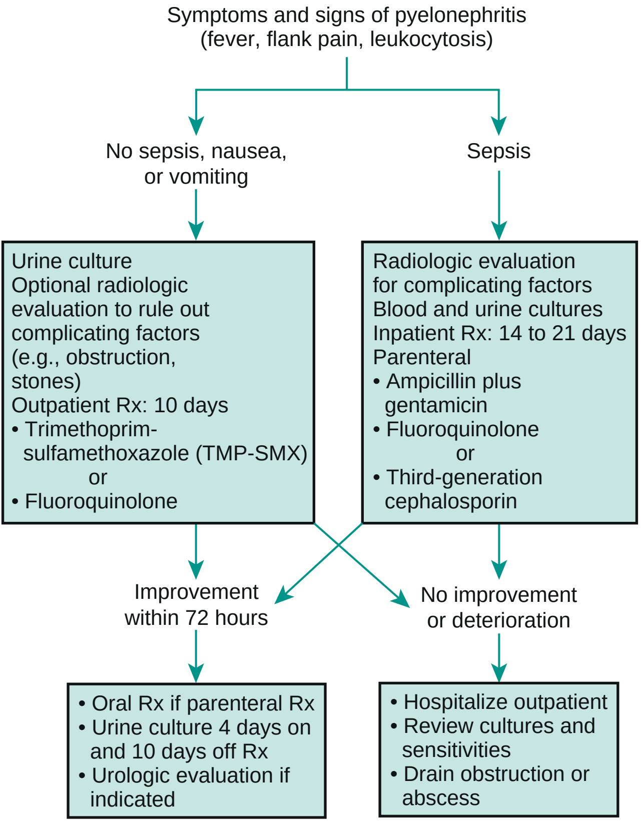
Symptoms and signs of pyelonephritis (fever, flank pain, leukocytosis)
No sepsis, nausea, or vomiting
Sepsis
Urine culture
Optional radiologic evaluation to rule out complicating factors (e.g., obstruction, stones)
Outpatient Rx: 10 days
• Trimethoprim-sulfamethoxazole (TMP-SMX)
or
• Fluoroquinolone
Radiologic evaluation for complicating factors
Blood and urine cultures
Inpatient Rx: 14 to 21 days
Parenteral
• Ampicillin plus gentamicin
• Fluoroquinolone
or
• Third-generation cephalosporin
Improvement within 72 hours
No improvement or deterioration
• Oral Rx if parenteral Rx
• Urine culture 4 days on and 10 days off Rx
• Urologic evaluation if indicated
• Hospitalize outpatient
• Review cultures and sensitivities
• Drain obstruction or abscess

FIGURE 3-3 **Management of acute pyelonephritis.** (From Schaeffer AJ, Schaeffer EM: Infections of the urinary tract. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders)

pending culture results. Many physicians administer a single parenteral dose of ceftriaxone, gentamicin, or a fluoroquinolone before initiating oral therapy.

Dehydration, vomiting, or sepsis may require hospitalization and parenteral administration of antibiotics (Box 3-3). A parenteral fluoroquinolone, a combination of ampicillin and gentamicin, or an extended-spectrum cephalosporin with or without an aminoglycoside is recommended. Antibiotics should be administered paren-

### BOX 3-3 **Guidelines for Parenteral Treatment of Pyelonephritis**

1. Clinical severity of infection, suspected urosepsis
2. Presence of underlying anatomical urinary tract abnormality
3. Inadequate access to follow-up care
4. Renal failure
5. Presence of urinary tract obstruction (infection behind an obstruction can be a lethal combination)
6. Immunocompromised and/or elderly host
7. Failed outpatient management on oral antimicrobials

terally until the patient is afebrile. They can then be switched to oral therapy. In the pregnant patient, ceftriaxone, aztreonam, or a combination of ampicillin and gentamicin can be administered with conversion to an oral cephalosporin when the patient is afebrile.

Therapy for uncomplicated pyelonephritis is generally recommended for 10 days, and a full 2-week course is recommended for those who present with sepsis. Complicated infection associated with hospitalization, catheterization, urologic surgery, or urinary tract abnormalities may require 3 weeks of antibiotic therapy along with associated urologic procedures to relieve obstruction that may be responsible for life-threatening sepsis.

## CLINICAL PEARLS

1. Differentiating upper urinary tract from lower urinary tract infection (UTI) is difficult clinically and often unnecessary because management is similar.
2. Recurrent UTI is not generally related to aspects of personal hygiene but is biological in origin.
3. Retroperitoneal ultrasonography is the best overall screening imaging study when investigating UTI.
4. Nitrofurantoin remains an excellent antibiotic for the short-term treatment of recurrent urinary infection but should not be used for long-term prophylaxis because of the slight risk of pulmonary fibrosis.
5. Don’t forget fosfomycin as an excellent antibiotic, especially when sensitivity panels show multiple antibiotic resistance and in patients with multiple antibiotic allergies.
6. Routine screening and treatment of asymptomatic bacteriuria (ASB) in the elderly is not indicated.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## Self-Assessment Questions

1. *How is colonization different than infection?*
2. *In what situations should asymptomatic bacteriuria (ASB) be aggressively treated?*
3. *How can recurrent urinary tract infections (UTIs) from bacterial reservoirs outside the urinary tract be managed?*
4. *The patient with persistent bacteriuria accompanied by flank pain, fever, and chills in the presence of an enlarged, nonfunctioning kidney with a stone or solid mass lesion should be suspected of having what disorder?*
5. *What important, potentially life-threatening condition must be ruled out in a patient with upper-tract urologic infection?*

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## CHAPTER 4

# Prostatitis and Lower Urinary Tract Infections in Men

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## Introduction

Lower urinary tract infections (UTIs) and inflammatory processes in the male involve the bladder, prostate, seminal vesicles, epididymides, testicles, utricle, Cowper gland, and glands of Littre. This chapter will focus on cystitis, prostatitis, epididymitis, and orchitis. However, it is important to note that since the conduits of the lower urinary tract and genital system are openly connected in the male, an infectious process of one organ has a potentially high ease of transmission to other components of these two systems.

## Bacterial Cystitis

### INCIDENCE AND RISK FACTORS

Most cases of acute bacterial cystitis occur when bacteria originating in the gastrointestinal (GI) tract travel up the urethra into the bladder. In the United States alone, UTIs account for over 7 million visits to physicians annually. These ascending infections are fairly common in women but less so in men, with a female to male ratio of 30:1. This is due to the substantial length of the male urethra compared to that of the female, thus providing protection from ascending pathogens. In infants, UTIs are more common in males than females with uncircumcised males having a higher rate than those that are circumcised.

**After age 50, the incidence of UTIs is similar in men and women.** Predisposing factors including indwelling Foley catheters, bladder neck obstruction, prostatic urethral obstruction, instrumentation, bladder diverticula, enteric fistulas, and urachal cysts; bladder stones; and other foreign bodies leave certain males at higher risk for bacterial cystitis and put older males at higher risk than younger ones. Diabetes mellitus can also lead to a neurogenic bladder with a large capacity and incomplete voiding, which leaves these males at a higher risk as well. If these infections are not treated appropriately, they can lead to upper tract damage and in some instances, sepsis and eventual mortality.

## SIGNS AND SYMPTOMS

Cystitis describes a clinical syndrome of dysuria, frequency, urgency, and occasionally suprapubic pain and/or hematuria. While this constellation of signs and symptoms points to cystitis from bacterial pathogens, other noninfectious conditions such as interstitial cystitis, bladder carcinoma, or calculi must be ruled out as well. On the other hand, not all of these symptoms need to be present for a man to have an active lower UTI.

## DIAGNOSIS

A detailed history and physical exam usually lead to a high suspicion of bacterial cystitis. When a high clinical suspicion exists, a urinalysis and a urine culture with antimicrobial sensitivities are used to confirm the diagnosis. The urine and the urinary tract are normally free of bacteria and inflammation. False-negatives can occur in the early phases of bacterial cystitis due to the low number of white blood cells and bacteria in relationship to dilute urine. False-positives occur most commonly due to contamination in specimen acquisition. While a clean-catch specimen is the most common method of culture, this leads to higher contamination rates. Urethral catheterized specimens and suprapubic aspirates lead to lower false-positive rates, but they are not as well tolerated as clean-catch specimens and are not indicated in men unless they are unable to void.

A proper voided specimen in circumcised men requires no special preparation. In uncircumcised men, the foreskin should be retracted and the glans penis washed with an antimicrobial liquid prior to collection. The Meares-Stamey test, while more often historically referenced than actually used in clinical practice, aims to identify the location of origin of a lower UTI. It is a four-glass test in which the first 10 mL of urine are collected as a urethral culture. After voiding 200 mL, a second sample is collected midstream that represents a bladder culture. At this point a prostatic massage is performed. The secretions are sent after being milked and collected in a sterile container. The next 10 mL of voided urine is then collected immediately after the massage. This represents a prostatic culture. The localization of bacterial flora identifies an infection as urethritis, cystitis, or prostatitis. **In a modified version that is more widely used in clinical practice, urine is taken before and after prostatic massage. This is known as the two-glass test.**

## URINALYSIS AND URINE CULTURE

Clean-catch urine sent for urinalysis provides vital information in diagnosing bacterial cystitis. Nitrite results only have a sensitivity of 50% but a specificity greater than 95%. Leukocyte esterase is a more sensitive test (approximately 80%), but is less specific (approximately 75%). If both a positive leukocyte esterase and nitrite are used to diagnose UTI, the specificity improves to 98%-100%, but the sensitivity declines to under 50% in some cases. On microscopic examination, the presence of more than 6 to 10 white blood cells per high-powered field indicates pyuria.

A colony count of greater than $10^5$ colony forming units (CFU)/mL of urine indicates a positive urine culture and diagnosis of an active bacterial infection in men rather than contamination. A gram stain is first reported and then a specific organism. If multiple organisms grow, then contamination should be suspected. Once sensitivities to antimicrobials are available, antibiotic therapy can be changed appropriately if prophylactic treatment was started.

## CYSTOSCOPY AND DIAGNOSTIC IMAGING

In otherwise normal middle-aged men who are sexually active, a further workup including imaging with a renal and bladder ultrasound or CT scan may not be required if the infection is eradicated after a course of antibiotics. In young patients who are not sexually active or in patients with a high clinical suspicion, further workup after treatment can be done to search for a urinary tract abnormality. This includes imaging to visualize the kidneys, ureters, and bladder, a cystoscopy, and a measurement of postvoid residual volume.

### TREATMENT

For bacterial cystitis, culture-confirmed antibiotics should be prescribed for 7-10 days. The most common outpatient antibiotics used are trimethoprim-sulfamethoxazole (TMP-SMX; Bactrim, Septra) with the usual dose being one double strength tablet twice a day, a quinolone such as ciprofloxacin 500 mg twice a day, and levofloxacin 250-500 mg once daily. In fungal cystitis with *Candida albicans* (more common in diabetics, immunocompromised men, or men with indwelling Foley catheters), oral fluconazole 50-100 mg daily can be used for 5-7 days. In more serious infections, continuous bladder irrigation with an antifungal agent may be required.

**CLINICAL PEARLS**

1. Bacterial cystitis is more common in women but can affect men, especially those with predisposing factors.
2. Urinalysis and urine culture are the mainstay of diagnostic testing when a clinical suspicion based on symptoms exists.
3. Treatment consists of a full course of antibiotics, with either TMP-SMX or a fluoroquinolone as first-line therapy.

## Prostatitis and Chronic Pelvic Pain Syndrome

### INCIDENCE AND RISK FACTORS

Prostatitis is one of the most common genitourinary causes of office visits for males. It accounts for about one fourth of visits due to lower urinary tract symptoms. This equates to about 2-3 million office visits to physicians every year. The particular causes of prostatitis vary based on the acuity of inflammation and the presence of a bacterial source. Risk factors of each cause vary, with those previously listed for bacterial cystitis playing a large part in the cases involving bacterial sources. However, bacterial infection accounts for only 10% to 15% of prostatitis-related lower urinary tract pathology.

### CLASSIFICATION AND SUBGROUPING

Prostatitis refers to several clinical syndromes. To simplify its classification, problems involving prostatic inflammation have been grouped into four distinct categories by the National Institute of Diabetes and Digestive and Kidney Diseases:

Category I: Acute bacterial prostatitis

Category II: Chronic bacterial prostatitis

Category IIIA/IIIB: Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CPPS)

Category IV: Asymptomatic inflammatory prostatitis

Each of these involves a different diagnosis criteria and treatment modality (Table 4-1).

TABLE 4-1 **Classification System for the Prostatitis Syndromes**

| Traditional | National Institutes of Health | Description |
|---|---|---|
| Acute bacterial prostatitis | Category I | Acute infection of the prostate gland |
| Chronic bacterial prostatitis | Category II | Chronic infection of the prostate gland |
| Non-applicable | Category III: Chronic pelvic pain syndrome (CPPS) | Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland employing standard methodology |
| Nonbacterial prostatitis | Category IIIA (inflammatory CPPS) | Significant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen |
| Prostatodynia | Category IIIB (noninflammatory CPPS) | Insignificant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen |

(*Continued*)

TABLE 4-1 **Classification System for the Prostatitis Syndromes—cont'd**

| Traditional | National Institutes of Health | Description |
|---|---|---|
| Non-applicable | Category IV: Asymptomatic inflammatory prostatitis (AIP) | White blood cells (and/or bacteria) in expressed prostatic secretions, postprostatic massage urine sediment (VB3), semen, or histologic specimens of prostate gland |

*(From Nickel JC: Prostatitis and related conditions, orchitis, and epididymitis. In Wein, AJ, Kavoussi, LR, Novick, AC, et al, CA editors:* Campbell-Walsh urology, *ed 10, Philadelphia, 2011, Saunders, pp*. 327–356.

## CATEGORY I: ACUTE BACTERIAL PROSTATITIS

Many of the same risk factors and symptoms for acute bacterial cystitis are encompassed by the symptomatology of acute bacterial cystitis. These infections are primarily caused by bacteria including *E. coli, Klebsiella, Pseudomonas, and Enterobacter.* Therefore risk factors for acute bacterial prostatitis are those that also contribute to UTI, such as difficulty emptying the bladder, indwelling Foley catheters, bladder neck obstruction, prostatic urethral obstruction, and instrumentation. A remote systemic site such as the nasal sinus, dental region, and the respiratory and GI tracts may be a subsequent cause of acute bacterial prostatitis through hematogenous or lymphatic spread. Intraprostatic urinary reflux into the ejaculatory and prostatic ducts can also contribute to the development of acute prostatitis.

Symptoms include dysuria along with voiding symptoms of frequency, urgency, and nocturia. Constitutional symptoms such as fever, chills, and malaise may also arise along with acute perineal and/or lower back pain. On physical examination the prostate feels enlarged and boggy with acute tenderness. However, digital rectal examination (DRE) should be limited if possible to prevent the occurrence of bacteremia. Patients usually have an elevated white blood cell count along with pyuria and bacteriuria on urinalysis. A urine culture is usually positive, with most cases caused by the organisms discussed above. One rare cause of prostatitis is the granulomatous type caused from miliary tuberculosis or systemic mycosis. A transrectal ultrasound (TRUS) may help in the diagnosis and evaluation, especially in those patients where a prostatic abscess is suspected. While many prostatic infections may be generalized throughout the gland, most are found in the peripheral zones due to the anatomical direction of the prostatic ducts.

The mainstay of therapy for men with acute bacterial prostatitis is antibiotic therapy with supportive care. Outpatient therapy consists of a 3-4 week course of TMP-SMX or a fluoroquinolone in those cases caused by common bacteria. Antibiotic therapy should be adjusted based on sensitivities on the urine culture. The patient is encouraged to stay well hydrated while taking antipyretics and analgesics. If urinary retention occurs, a suprapubic tube should be used for drainage to avoid further trauma to the prostate and spread of infection. If the patient is acutely ill, inpatient therapy is warranted with hydration and intravenous antibiotic therapy. Tuberculous and mycotic prostatitis are treated with antitubercular and antifungal therapies respectively. If a prostatic abscess develops, the patient may require abscess drainage via either transurethral unroofing of the abscess or transrectal drain placement.

## CATEGORY II: CHRONIC BACTERIAL PROSTATITIS

Chronic bacterial prostatitis is generally manifest by periods of complete lack of symptoms punctuated by recurrent acute culture-documented UTIs with the same organism from periodic seeding of bacteria ensconced in the interstices of the prostate. Occasionally symptoms of chronic bacterial prostatitis may include perineal, pelvic, or low back pain along with dysuria and irritative voiding symptoms. The same bacteria that cause acute prostatitis are those that lead to the chronic type, with *E. coli* being the most common pathogen.

A history and physical exam should be performed to rule out other pathology. Blood tests such as a CBC and a PSA are not helpful in the diagnosis. PSA levels are typically increased due to prostatic inflammation. To confirm its diagnosis, pathogenic bacteria and white blood cells are localized to prostate-specific specimens. This is done through the Meares-Stamey test, or more simply, a pre- and postmassage test (PPMT) of the prostate.

Due to their unique and favorable pharmacokinetic properties and broad coverage, fluoroquinolones are the first- line antimicrobial therapy for chronic bacterial prostatitis, with TMP-SMX used as well. A 4-6 week course is curative in up to 50% of patients. For those who continue to be culture positive, treatment can be extended to up to 12 weeks. Even after treatment courses, recurrent bacteriuria is common, and some patients are placed on daily prophylaxis to curtail acute flares. For patients with lower urinary tract symptoms or other forms of prostatic obstruction, alpha-blockers have been suggested to reduce recurrence rates.

## CATEGORY IIIA/IIIB: CHRONIC NONBACTERIAL PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

Symptoms in patients with CPPS are generally chronic as opposed to the intermittent symptoms of chronic bacterial prostatitis. These patients are characterized as having pelvic pain (perineal, suprapubic, penile, and/or testicular), lower urinary tract symptoms, and sexual dysfunction (most often pain with ejaculation). All of this is present in the absence of uropathogenic bacteria. It can be further divided into an inflammatory subtype (IIIA) or noninflammatory subtype (IIIB) based on the presence or absence of white blood cells in prostate specific specimens. The use of The National Institutes of Health Chronic Prostatitis Symptom Index (Figure 4-1) is useful in the accurate diagnosis of CPPS. This also helps in tracking the patients' symptoms during therapy.

The exact etiology of CPPS is unclear. One proposed theory is a cascade of events which leads to an immunological response and inflammatory reaction. This cycle of events recurs with a persistent reactivation of symptoms caused by the response. Symptoms are worsened by proposed neuropathic damage from the continued cycle. Other theories center on neurologic and/or psychologic factors.

Patients with CPPS must first be evaluated to rule out other causes of symptoms, most importantly bacterial causes, malignancy, or other reversible cause. A urine culture should be sent along with urine cytology if the patient has hematuria. Some

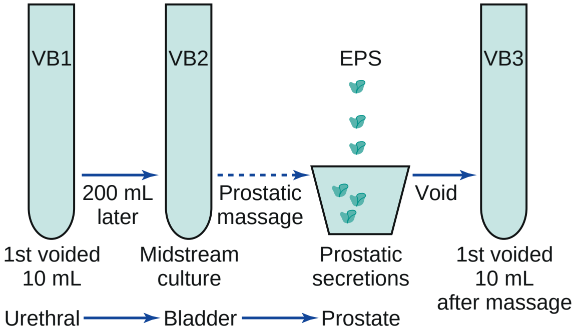

FIGURE 4-1 NIH-Chronic Prostatitis Symptom Index (NIH-CPSI).

patients may benefit from urodynamic studies. Each patient should then be given the NIH-CPSI to fill out.

For those diagnosed with CPPS, treatment is multifactorial. Some patients with the inflammatory subtype (IIIA) still benefit from 4-8 week course of antibiotics. Other treatment for subtype IIIA include prostatic massage, use of alpha-blockers, antiinflammatory drugs, or immune modulators. For patients with category IIIB, a mixture of analgesics, muscle relaxants, and alpha-blockers has been successful in treating bothersome symptoms. Biofeedback, relaxation exercises, and pelvic floor physical therapy with myofascial trigger-point release and Thiele massage may help other patients. Surgical treatment (endoscopic incision of the bladder neck, insertion of neuromodulation devices) should only be used in patients that have specific identifiable causes of symptoms such as urodynamic or cystoscopic findings. In some cases, a cure for these patients is impossible, so therapy should be directed to alleviating symptoms as much as possible.

## CATEGORY IV: ASYMPTOMATIC INFLAMMATORY PROSTATITIS

Patients with category IV prostatitis require no treatment because they are asymptomatic and have no bacterial infection to eradicate. The diagnosis is based on pathology specimens initiated by a rising PSA or abnormal DRE showing the presence of white blood cells.

## CLINICAL PEARLS

1. Prostatitis refers to inflammation of the prostate. This can be due to multiple causes, which have been categorized by the National Institute of Diabetes and Digestive and Kidney Diseases:
    - Category I: Acute bacterial prostatitis
    - Category II: Chronic bacterial prostatitis
    - Category IIIA/IIIB: Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CPPS)
    - Category IV: Asymptomatic inflammatory prostatitis
2. Bacterial prostatitis refers to an infection of the prostate, either acute or chronic. The treatment of each centers on eradication of the bacteria with antimicrobial agents.
3. A patient with no history of a culture-documented urinary tract infection (UTI) is unlikely to have a diagnosis of chronic bacterial prostatitis.
4. Nonbacterial forms of prostatitis can be inflammatory or noninflammatory. Symptom relief is the main focus of treatment. The exact etiology is unknown, and treatment algorithms vary based on specific patient complaints and relief patterns.

# Epididymitis and Orchitis

Acute epididymitis is an infection of the epididymis that most commonly results from the retrograde migration of bacteria from the distal urethra down into the ejaculatory duct and vas deferens. While most common in the adolescent and elderly populations, it can affect males of any age. **In patients under the age of 35, the most common form of transmission is sexually with the two most common pathogens being *C. trachomatis* and *N. gonorrhoeae*.** In patients who have had anal intercourse, enteric bacteria may be the cause. In the elderly, *E. coli* and *Pseudomonas* species are the most common offending pathogens. Indwelling catheters heavily contribute to the development of epididymitis in the elderly population through a retrograde mechanism.

Antegrade descent may also occur. Infections originate from the bladder and, due to problems such as bladder outlet obstruction or poor bladder emptying, ascend to the epididymis. Patients who have undergone cystoscopic procedures, notably transurethral resection of the prostate, are at greater risk of epididymitis spread in this fashion. Other rarer forms of acquisition are hematogenous spread of bacteria from a remote source and the use of amiodarone because it is selectively concentrated in the epididymis and can cause inflammation.

Patients with acute epididymitis often present with a tender hemiscrotum and a swollen epididymis that can be up to 10 times the normal size. The scrotum is often warm, erythematous, and swollen. A heavy, dull ache can sometimes radiate to the ipsilateral flank. The patient may have associated fevers, chills, and voiding symptoms. In some cases a reactive hydrocele forms due to a reaction of the tunica albuginea to the severe inflammation. If the infection is present for a prolonged period, it may spread to the testicle, progressing to epididymo-orchitis.

Along with a thorough history, a thorough physical exam should be performed. Palpation of the testicle reveals pain while elevation may relieve it. The spermatic cord may be tender as well. The urethral meatus should be inspected for discharge. The scrotum should be inspected for the presence of an abscess. A urinalysis and urine culture should be sent. If sexual transmission is suspected, a urethral swab for *C. trachomatis* and *N. gonorrhoeae* should be sent. A scrotal ultrasound should be obtained to rule out other causes of acute scrotal pain such as testicular torsion in the age-appropriate population. Doppler flow on the ultrasound will reveal increased blood flow to the epididymis in acute epididymitis.

All patients should be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), ice to the scrotum, and scrotal elevation. If a bacterial source is identified, appropriate antibiotics are administered. If the offending pathogen is from a urinary source, a 10–21-day course of TMP-SMX or fluoroquinolone is first line-therapy and should be tailored to final culture results. If *C. trachomatis* or *N. gonorrhoeae* infection is suspected, patients should be treated for both. *C. trachomatis* is treated with an initial dose of 200 mg of doxycycline and 100 mg twice daily for 10 days thereafter. *N. gonorrhoeae* is treated with a one-time intramuscular 250 mg dose of ceftriaxone or 500 mg of ciprofloxacin by mouth. If a scrotal abscess is present, incision and drainage may be required to further clinical improvement.

Orchitis results from involvement of the testicle in the inflammatory or infected process involving the epididymis. Its evaluation and treatment are essentially the same with antibiotic therapy, when positive urinalysis and culture data exists, and supportive therapy in all cases. If abscess or necrosis develops, surgical intervention including orchiectomy may be indicated.

Pure isolated orchitis is rare and usually of viral etiology such as in mumps orchitis. It is transmitted via a hematogenous route. Other infectious etiologies may be from infectious mononucleosis, mycobacterium, or fungal sources.

## CLINICAL PEARLS

1. Acute epididymitis most commonly occurs from retrograde migration of bacteria into the epididymis from the urethra. Other forms of transmission also exist.
2. Patients usually present with a painful, warm hemiscrotum with associated voiding and constitutional symptoms. Scrotal ultrasound reveals increased blood flow to the head of the epididymis.
3. Treatment consists of antibiotic therapy to eradicate the bacteria and supportive care including NSAIDs and applying ice to and elevating the scrotum.
4. Epididymitis in the under-35 age group is often empirically treated with a tetracycline pending culture results.

## DIFFERENTIAL DIAGNOSIS

***For men with lower urinary tract symptoms along with infectious signs:***

Acute bacterial cystitis
Acute pyelonephritis
Bladder cancer
Acute bacterial prostatitis
Prostatic abscess
Chronic bacterial prostatitis
Chronic nonbacterial prostatitis
Chronic pelvic pain syndrome (CPPS)

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## Self-Assessment Questions

1. *What urinalysis findings aid in identifying those men with a high likelihood of urinary tract infection (UTI)?*
2. *What are the most common pathogens to cause UTIs and acute bacterial prostatitis in men?*
3. *What are the most common risk factors for bacterial prostatitis in elderly men?*
4. *If urinary drainage is required in a man with acute bacterial prostatitis, what type of catheter should be placed?*
5. *What differentiates chronic nonbacterial prostatitis from chronic pelvic pain syndrome (CPPS)? How should each be treated?*
6. *What are the most common risk factors for epididymitis in the younger population?*
7. *What are the mainstays of treatment for men with acute epididymitis?*

## SUGGESTED READINGS:

1. Meares EM Jr, Stamey TA: Bacteriologic localization patterns in bacterial prostatitis and urethritis, *Invest Urol* 5:492, 1968.
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5. Schaeffer AJ, Schaeffer EM: Infections of the urinary tract. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh Urology*, ed 10, Philadelphia, 2011, Saunders, pp 257–326.

## CHAPTER 5

# Specific Infections of the Genitourinary Tract

Joseph F. Harryhill, MD, FACS

## Genitourinary Tuberculosis

### GENERAL CONSIDERATIONS: SCOPE OF THE DISEASE

- One of the oldest infections afflicting humankind and often called the great imitator, tuberculosis (TB) is not a disease of the past. Instead, the incidence of infections related to mycobacterial organisms (*Mycobacterium tuberculosis*, *avium* complex, and *leprae*) were until recently on the rise worldwide. The World Health Organization reported 8.7 million new cases of tuberculosis in 2011.
- Tuberculosis (consumption) reached epidemic proportions in 18th century Europe. Signs of the disease have even been found in mummies dating back to 3000 BCE.
- The bacillus causing tuberculosis was identified by Robert Koch in 1882.
- Once infected, 5% to 10% of patients exposed to TB will develop active disease in their lifetime. Those with compromised immune systems are at higher risk to become symptomatic.
- The largest number of new cases occurs in Asia, but the highest per capita incidence of new TB cases is in sub-Saharan Africa.
- In 2011, 1.4 million persons died of tuberculosis; over 95% of deaths occurred in developing nations.
- TB is a major cause of mortality in persons infected with the human immunodeficiency virus (HIV), causing one fourth of all deaths. Tuberculosis is the most important opportunistic infection in this patient group.

- One third of the world's population has latent TB. Those who are not ill generally cannot transmit the disease.
- The genitourinary tract is the second most common extrapulmonary site of involvement, after lymph nodes. Active genitourinary TB presents 5 to 25 years after initial infection.

## PATHOGENESIS

- Tuberculosis is spread most commonly from person to person through inhalation of aerosolized droplets containing bacteria. The disease is efficiently transmitted, requiring only a few inhaled bacteria.
- Host immunity largely determines whether infection occurs or is eliminated at the initial exposure. If not eliminated, mycobacteria then slowly divide within alveolar macrophages, and it takes several weeks before a cellular immune response is mounted. Before the host immune system can limit or destroy the bacteria, hematogenous spread can occur.
- Medlar proved in 1949 that the infection spreads from the lungs to the renal cortex by hematogenous dissemination. The kidney is usually the primary organ infected. The renal cortex is favored because of higher oxygen availability. Other parts of the GU tract become involved by direct extension.
- Primary sites of genital tract disease include the epididymis in males and the fallopian tubes in females.
- At infected foci, lymphocytes, and fibroblasts aggregate to form a granuloma around the bacilli, but the organisms may remain viable and become dormant within the tubercle, resulting in latent infection.
- Involved sites may remain dormant for many years, then reactivate and spread by caseation and cavitation. Factors favoring reactivation include diabetes, HIV, malignancy, chemotherapy, or immunosuppressant medications.
- Tubercles in the glomeruli may cause parenchymal destruction, then spread into the medulla and result in papillary necrosis or cavitation. Bacilli then enter the urine and travel down to the ureters and bladder. The bacilli in the ureters can cause fibrosis resulting in ureteropelvic junction (UPJ) obstruction, ureteral stricture, and bladder inflammation and contracture.

- From the lower urinary tract, passage of infected urine into the genital ducts then leads to involvement of the prostate, seminal vesicles, vas deferens, epididymis, and testicle.
- Genitourinary TB can also arise from infection and dissemination of attenuated bacilli during intravesical bacillus Calmette-Guérin (BCG) therapy for treatment of urothelial carcinoma. In rare cases miliary TB has been reported as a complication of BCG instillation.

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

- Genitourinary TB has varied presentations, but irritative voiding symptoms are commonly reported (50%). Cystitis symptoms may persist despite antibiotic therapy. Hematuria and mild flank pain are present in one third of patients.
- Renal involvement may be silent, with only nonspecific symptoms; cases of GU tuberculosis can thus be easily overlooked.
- Symptomatic GU tuberculosis is more common in males (2:1), and the earliest signs of infection may be tuberculous epididymitis or cystitis.
- Granulomatous prostatitis may occur and is also seen following intravesical therapy with BCG.
- Female genital TB can present as infertility, nonspecific pelvic pain, or menstrual alterations. Fallopian tubes are involved in 95% of women with genital TB, where the disease may then spread to the peritoneum.
- Definitive diagnosis involves demonstration of mycobacterial organisms in urine culture or histopathologic examination of a biopsied granulomatous lesion.
- Majority of patients present with “sterile pyuria”; 20% may have superimposed bacterial infections.
- Three to five early-morning urine specimens are preferred because excretion of the organism may be sporadic. Incubation of urine cultures for up to 1 week is required to visualize early colonies on agar-based culture media.
- Cultures are essential to determine antibiotic sensitivity but may take up to 6 to 8 weeks.
- Polymerase chain reaction (PCR)-based nucleic acid amplification tests of the urine are reliable, specific, and provide

rapid results in diagnosis of tuberculosis. There is a 10% false negative rate. These assays are best used in conjunction with cultures and clinical symptoms to confirm the diagnosis of genitourinary TB.

- The Mantoux PPD (purified protein derivative) tuberculin skin test, which is based on a delayed-type hypersensitivity reaction to intradermal injected antigen, is useful when positive, and a negative TB tine test makes the diagnosis unlikely.
- Radiographic findings in genitourinary TB are nonspecific but are important to evaluate extent of disease. Plain radiographs (kidneys-ureters-bladder [KUB], chest x-ray) may show calcification. Intravenous pyelogram (IVP) or computed tomography (CT) urography can demonstrate parenchymal destruction and assess for obstruction. CT imaging can also identify adrenal involvement (5% of active TB cases).
- In patients with genitourinary TB, 50% to 75% have chest radiographs that show old or active pulmonary disease.
- Cystoscopy is rarely indicated for diagnostic purposes but may be needed to rule out malignancy. Bladder biopsy can cause dissemination of the disease in patients who are not on antituberculous therapy.

## THERAPY

1. General considerations
   - Successful treatment requires early diagnosis and initiation of antituberculous chemotherapy. Multiple drugs work synergistically and prevent development of drug resistance.
   - Drug sensitive TB is treated with a standard 6-month course, starting with four antimicrobial agents for 1 to 2 months. Then an additional 4 months of rifampin and isoniazid (INH) are used.
   - Surgical intervention may be necessary for treatment of obstructing lesions or removal of infected tissue (e.g., nonfunctioning renal unit) but should be deferred for 4 to 6 weeks after starting medical therapy.
   - Supervised, directly observed administration of the medications is recommended to ensure compliance.

- Reevaluation with cultures is recommended 3, 6, and 12 months after completion of therapy, with appropriate imaging studies in patients with genitourinary involvement.
- Multidrug-resistant TB is most often treatable and can be cured with use of second-line agents.

2. **Primary agents** include INH, rifampin, pyrazinamide and ethambutol (Table 5-1). Pyridoxine (vitamin B6, 10 to 50 mg daily) should be taken with regimens that include INH to prevent central nervous system (CNS) effects and peripheral neuropathy.
3. **Second-line agents** include aminoglycosides (streptomycin, capreomycin, kanamycin, amikacin), cycloserine, ethionamide, fluoroquinolones (levofloxacin, moxifloxacin [Avelox]), aminosalicylic acid, and protionamide.

TABLE 5-1 **First-Line Antituberculous Chemotherapeutic Agents**

| Drug | Dose | Side effects | Remarks |
|---|---|---|---|
| Isoniazid (INH) | 5-10 mg/kg, up to 300 mg/day, PO or IM | Peripheral neuritis, hepatitis | Pyridoxine for prevention of neuritis; monitor liver function tests |
| Rifampin | 10-20 mg/kg, up to 600 mg daily, PO | Hepatitis, hypersensitivity, purpura (rare) | Orange discoloration of urine |
| Pyrazinamide | 25 mg/kilogram, up to 2 g daily, PO | Hyperuricemia, hepatotoxicity | Monitor LFTs |
| Ethambutol | 15-25 mg/kg daily, PO | Optic neuritis, skin rash | Baseline visual acuity and color discrimination test |

Twice-weekly dosing schedules for INH, rifampin, and ethambutol are also available. Primary resistance to INH therapy is uncommon in the United States, but is prevalent in Asia, Africa, and Central America.

# Genitourinary Schistosomiasis

## GENERAL CONSIDERATIONS

- An estimated 300 million people are infected worldwide by schistosomiasis, also known as *bilharzial disease*. The parasitic *Schistosoma* trematodes use freshwater snails, not found in the United States, as intermediate hosts.
- There are four species of *Schistosoma* that can cause human infection. *Schistosoma hematobium* is the pathogen responsible for urinary schistosomiasis, with paired adult worms residing in the perivesical venules.
- Genitourinary schistosomiasis is endemic to Africa and the Middle East.
- GU infection by *S. hematobium* leads to hematuria, hydronephrosis, and carcinoma of the bladder. Affected females may have cervicitis and vaginitis, and late manifestations of the female genital tract include infertility and ectopic pregnancy.
- The urinary bladder develops sandy "patches" containing schistosome eggs; later in the infection, calcification of these patches occurs. The presence of a calcified bladder on plain radiograph or CT is diagnostic of chronic urinary schistosomiasis (see Figure 5-1).

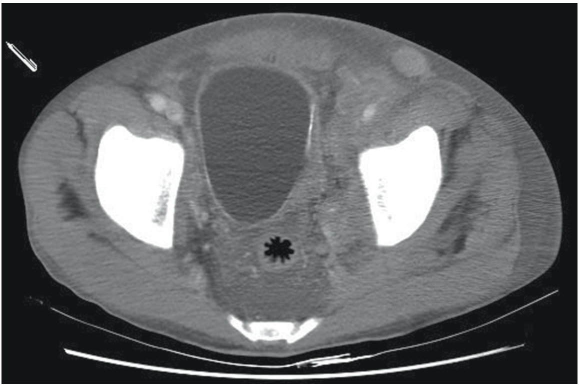

**FIGURE 5-1 Submucosal bladder calcification seen on CT in patient with known history of urinary schistosomiasis.** (Image courtesy of Parvati Ramchandani, MD, University of Pennsylvania.)

## ETIOLOGY AND PATHOGENESIS

- Infected snails release cercariae that penetrate human skin or mucous membranes in contact with fresh water.
- Larvae migrate through the body and mature into adult male and female worms. The worms, 1 to 2 cm in length, pair and reside in the vesical venules. The female releases 200 to 300 eggs per day into the submucosa of the bladder, a process that can continue for several years. Some of the eggs are excreted in the urine to complete the life cycle, returning to water and the intermediate snail host.
- The ova deposited into the bladder submucosa produce an intense inflammatory reaction.
- Diagnosis of schistosomiasis can be made by observing schistosome ova in the urine. Terminally spined eggs found in the urine sediment are pathognomonic of *S. hematobium*, and this remains the gold standard for diagnosis of active infection.
- Rectal or bladder biopsy can also be performed for diagnostic purposes.
- Serology tests are also available through the Centers for Disease Control and Prevention but cannot distinguish between previous exposure and acute or chronic infection.
- Imaging studies are important to assess for possible obstruction.

## CLINICAL FEATURES

- Initial contact with cercariae can produce intense pruritus (swimmer's itch).
- After larvae gain access to the systemic circulation, symptoms include fever, cough, malaise, and myalgia. Heavy inoculation can rarely produce a serum sicknesslike syndrome that can be fatal.
- Most human hosts become chronically infected, and female worms may produce eggs for years, causing slowly progressive disease.
- The eggs elicit a granulomatous inflammatory response that accounts for the typical initial symptoms of painful terminal hematuria, dysuria, hematospermia, and irritative voiding symptoms.

- Schistosomal bladder polyps, secondary infection (often by *Salmonella* species), and urinary tract calcification occur. In some patients, polypoid lesions in the bladder can cause significant hematuria, clot retention, and anemia.
- Late complications include fibrosis of the bladder, urethra, and distal ureters that can lead to bladder contraction and upper tract deterioration. Obstructive uropathy is often asymmetrical.
- Schistosomal contracted bladder syndrome presents as lower abdominal and pelvic discomfort, urinary frequency, and urge incontinence. Bladder capacity may be severely compromised.
- After some years, the active infection may become quiescent, with less pain as polypoid lesions are replaced by fibrosis; silent obstruction may occur.
- Bilharzial bladder cancer typically has earlier onset (age 40 to 50) compared to transitional cell urothelial malignancy and usually presents as squamous cell carcinoma (60% to 90%) or adenocarcinoma (5% to 15%).
- Nearly half of these tumors are superficial and exophytic, with a fairly good overall prognosis with surgery and treatment of the underlying infection.

## THERAPY

- Praziquantel is the medical treatment of choice for all schistosoma infestations, and it results in high cure rates. Metriphonate is also effective against *S. hematobium*.
- Recommended treatment with praziquantel is 40 mg/kg given in one day in a single or divided dose. The medication is generally well tolerated, with few side effects (occasional headache, dizziness, fever).
- Praziquantel is highly active in all stages of the disease, and medical therapy should be administered before surgical intervention.
- Surgery for management of chronic obstructive uropathy may be required, including possible bladder augmentation or urinary diversion in cases of severely contracted bladder. Ureteral dilation or reimplantation may be necessary. Some patients require surgery for chronic epididymitis.
- Endoscopic intervention may also be indicated urgently in cases of severe hemorrhage but should also be preceded by antibiotic therapy whenever possible.

## Genital Filariasis

### GENERAL CONSIDERATIONS

- Tissue nematode infections are widespread in tropical countries. WHO reports that 120 million people are infected by *Wuchereria bancrofti,* the organism responsible for 90% of cases of human lymphatic filariasis. Of those infected, over 25 million men have genital disease.
- Elimination of lymphatic filariasis in the Americas is on CDC's list of "winnable battles" (http://www.cdc.gov/winnablebattles/) - health conditions that have large scale impact but with known, effective strategies for management and disease reduction.
- *W. bancrofti* is a human parasite with no intermediate animal reservoir. Infection occurs when filarial parasites are transmitted via mosquito bite from an insect that contains larvae.
- Lymphatic filariasis can also rarely be caused by *Onchocerca volvulus* or *Brugia malayi*.
- Although human filariasis is not endemic in the United States, filarial infection is the most common cause of eosinophilia in Caucasians returning from sub-Saharan Africa. Short-term tourists have a low risk of contracting chronic filariasis.

### ETIOLOGY AND LIFE CYCLE

- When a human is infected, larvae migrate to lymphatic vessels and mature. Adult filariae in the lymphatic system can live for years, and are generally resistant to host immune attack. *W. bancrofti* worms prefer periaortic, iliac, and scrotal lymphatics.
- Male and female worms mate, and the female releases larvae (microfilariae) into the bloodstream in a diurnal pattern. In fact, the timing of microfilaremia in the human host (usually midnight) is synchronized to the peak feeding times of the local mosquito vector.
- These larvae are transmitted to the insect host during a blood meal, completing the life cycle.

### PATHOGENESIS AND CLINICAL FEATURES

- Lymphangitis and lymphadenitis are usually the presenting symptoms of early filarial infection. The acute syndrome, which can also include fever and malaise, lasts days or weeks, and a single episode will usually resolve without sequelae.

- Conversely, obstructive lymphatic disease occurs in humans who are repeatedly bitten and reinfected by mosquitoes over months to years.
- When adult worms die, they provoke a severe inflammatory response, leading to funiculo-epididymitis/orchitis, lymphangitis, and filarial abscess. Scarring and lymphatic obstruction occurs, and large hydroceles and scrotal and penile elephantiasis are dramatic complications of late infection.
- Histological examination of resected nodules shows large granulomas surrounding necrotic filariae.
- Chronic filariasis can manifest in one of four ways:
  - Asymptomatic infection: In fact, most infected individuals never develop clinical symptoms despite persistence of the parasite.
  - Episodic "filarial fevers": Medical therapy is effective at this stage, but untreated patients who remain in the endemic area will likely progress to chronic infection with possible lymphedema.
  - Chronic filariasis with progressive lesions: These include funiculoepididymitis, hydrocele, and chyluria. (When chronic scarring from tissue damage occurs, these conditions do not resolve with medical therapy.)
  - Tropical pulmonary eosinophilia, an asthmalike condition with lung infiltrates: These patients usually do not have chronic GU lesions but can have marked lymphadenopathy. This syndrome occurs more frequently in infected persons in Asia.

## DIAGNOSIS

- Filariasis should be suspected in any patient with lymphedema or hydrocele who dwells in an endemic area. Definitive diagnosis can be challenging.
- Although identification of adult worms in tissue is diagnostic, it is more common to detect microfilariae in peripheral blood. Highest yield occurs when the sample is obtained at midnight. Release of microfilariae into the circulation by administration of diethylcarbamazine (DEC) can also aid in the diagnosis. Microfilariae may be absent in early or late disease and in patients with tropical pulmonary eosinophilia.
- Antibody and antigen tests and molecular assays to detect parasitic DNA have also been developed.

## DRUG THERAPY

- Diethylcarbamazine is an effective microfilaricide and can also kill some adult worms. The drug has been available for more than 50 years. (DEC is not FDA approved in the United States and must be obtained through the CDC.) It can be administered either as a 1-day treatment (6 mg/kg/day), or a 12-day course. Toxicity depends upon the level of microfilariae in the bloodstream; initial dose reduction or pretreatment with corticosteroids and antihistaminics may be required in heavily infected subjects.
- Ivermectin is also effective against microfilariae. However, it has no effect on adult worms which are responsible for the chronic lymphatic manifestations of filariasis. It is administered in a single dose of 200 to 400 mcg/kg.
- Albendazole, a broad-spectrum antihelminthic, kills both microfilariae and adult worms. It is administered as a single dose of 400 mg orally (PO).
- Doxycycline has shown to be effective in killing adult worms, with a 4- to 6-week course, 200 mg per day.
- Suramin and mebendazole have also been used as antihelminthic therapy in treatment of filariasis.

## TREATMENT PRINCIPLES

- Mass treatment programs are focused on reducing microfilariasis with antihelminthics (DEC, ivermectin, or albendazole), and reduction of mosquito vectors in endemic areas. WHO recommends single-dose annual drug administration to entire at-risk populations for 4 to 6 years in endemic areas to fully interrupt disease transmission.
- DEC should be used with caution in patients at risk for onchocerciasis (river blindness) or *Loa loa* infection because of risk of severe adverse reactions.
- Patients with chronic severe filarial lymphedema do not respond well to medical therapy because infection is usually no longer active. In these patients, use of compression stockings and leg elevation is important in reducing severity and progression of lymphedema. Simple measures of hygiene and skin care can reduce risk of secondary infection.

- In some patients, surgical intervention may be necessary, including orchiectomy and cord excision for recurrent funiculo-epididymitis, hydrocelectomy for large symptomatic hydroceles, and removal of redundant scrotal or vulvar tissue with reconstruction for severe elephantiasis.

## Rare Parasitic Genitourinary Infections

### HYDATID DISEASE (ECHINOCOCCOSIS)

- Hydatid disease of the kidney is very rare and caused by the larval stage of *Echinococcus granulosus*. This intestinal tapeworm affects dogs and is endemic to sheepherding regions of the world.
- After a human ingests food contaminated by the parasite's eggs, the larval form penetrates intestinal mucosa and travels to the liver, the most frequent site of primary disease. Subsequent pulmonary or systemic spread may later occur. Renal involvement accounts for only 2% of hydatid disease cases.
- Presenting signs include abdominal mass or nonspecific flank pain. Cysts can slowly increase in size up to 20 cm or more; however, rupture is rare. Cysts frequently involute and become calcified.
- CT imaging shows a thick-walled, septate cystic lesion with a diagnostic rosette or honeycomb pattern. Curvilinear calcification may be seen on KUB.
- Aspiration of the cysts in confirmed cases is not recommended because of risk of rupture and spillage of cyst fluid which may cause an anaphylactic reaction and metastatic seeding.
- Medical therapy with mebendazole or albendazole has been used with limited success, but prolonged therapy carries risk of significant side effects, including hepatotoxicity.
- Surgical removal of the renal hydatid cyst should be done without rupture. Surrounding structures should be protected with saline-soaked pads or towels. Pretreatment with praziquantel and albendazole is suggested for 7 to 10 days prior to surgical intervention. Nephron-sparing surgery is recommended.

### AMEBIASIS

- Amebiasis is caused by the single-cell parasite *Entamoeba histolytica*. This disease is prevalent in developing countries with poor sanitary conditions. Infection occurs by consumption of fecally contaminated food or water.
- Amebiasis is a rare cause of renal abscess, more frequently involves the right kidney, and occurs in association with liver abscess. Renal vein thrombosis has been reported.
- Diagnosis can be challenging and requires identification of the parasite in stool samples; serum antigen and PCR tests are also available when systemic infection is suspected.
- Medical therapy with metronidazole or tinidazole is effective; surgery for management of abscess should be delayed until drug therapy has been initiated.

## Genitourinary Fungal Infections

### GENERAL CONSIDERATIONS

- Mycotic (fungal) infections pose an increasing threat to public health, with a rise in incidence of opportunistic infections in immunocompromised hosts and of hospital-associated infections.
- The incidence of fungal urinary tract infection (UTI), in particular, has increased, partly caused by widespread use of antimicrobial agents, and can occur with prolonged or inappropriate use of urinary drainage catheters.
- Opportunistic infections, including candidiasis, cryptococcosis, and aspergillosis, occur in transplant and cancer patients and those with HIV or acquired immunodeficiency syndrome (AIDS). *Candida* is the most prevalent of the fungi and accounts for the majority of mycotic infections involving the urinary tract. Evaluation and treatment of these opportunistic infections is considered below.
- Community-acquired, primary fungal infections, including coccidiomycosis (valley fever), blastomycosis, and histoplasmosis, are caused by fungi that are abundant in the environment and endemic to the United States. These present typically with systemic, flulike illness, with occasional involvement of the genitourinary tract.

## CANDIDIASIS

1. Pathogenesis and clinical manifestations
    - *Candida* species normally inhabit mucocutaneous body surfaces. Urine cultures in hospitalized patients are often positive for candiduria, most likely reflecting colonization of the bladder or an indwelling urinary catheter. The majority of patients are asymptomatic.
    - The risk of developing a complicated UTI in patients with candiduria is low, but risk increases if obstruction is present or instrumentation of the urinary tract is performed.
    - The finding of yeast in the urine could also indicate the presence of hematogenous seeding of the upper urinary tracts from disseminated candidiasis, particularly in immunosuppressed patients or neonates. Compromised newborns with positive urine cultures are at high risk of developing obstructing fungus balls in the collecting system.
    - Candidemia is an important cause of nosocomial bloodstream infection in the United States, accounting for approximately 10% of all cases. Mortality in adult patients with candidemia is nearly 50%.
2. Diagnosis
    - Although the diagnosis of bacterial UTI is standardized, relying on laboratory findings of pyuria and a certain minimum count (colony-forming units) of bacteriuria, similar guidelines do not exist in establishing diagnosis of urinary infection due to *Candida* species.
    - In a patient with systemic illness, both blood and urine cultures must be evaluated along with overall clinical assessment of the patient.
    - Upper tract imaging (ultrasound or CT) should be considered to rule out obstruction, abscess, or fungal bezoar.
3. Treatment
    - Asymptomatic candiduria generally resolves when predisposing factors (antibiotics and indwelling catheters) are discontinued.
    - However, in high-risk patient populations (infants with very low weight at birth, neutropenic patients, transplant recipients, and symptomatic patients with

fever), antifungal therapy is recommended. Candiduria in a neutropenic patient is a strong predictor of disseminated candidiasis, necessitating systemic therapy.
- Symptomatic vesical candidiasis can be treated with intravesical agents, such as amphotericin B or miconazole irrigation (50 mg/1000 mL continuous bladder infusions), or oral flucytosine, 50 to 75 mg/kg/day as long as upper tract or invasive disease is excluded.
- Treatment of pyelonephritis or disseminated candidiasis requires fluconazole (IV or PO), intravenous caspofungin, amphotericin B, or fluconazole-amphotericin B combination therapy.

## ASPERGILLOSIS

- *Aspergillus* species are ubiquitous, and exposure occurs through inhalation of spores.
- Pulmonary illness occurs, and severity of the disease depends upon the status of the host.
- In immunocompromised patients, disseminated infection can occur. Genitourinary infection is a manifestation of systemic disease. Abscess or obstruction caused by fungal bezoars can occur in the kidneys.
- Rare cases of prostatic aspergillosis with abscess have been reported, presenting as bladder outlet obstruction.
- Medical therapy options include voriconazole, amphotericin B, and caspofungin, with combination therapy recommended in immunosuppressed patients.

## CRYPTOCOCCOSIS

- Cryptococcosis is caused by the soil-based fungus *Cryptococcus neoformans* and is one of the most common opportunistic infections in HIV patients, often fatal even with treatment. Infection can also occur with other underlying conditions such as diabetes mellitus or systemic lupus erythematosus.
- The most commonly involved sites are the lungs and CNS (cryptococcal meningitis). Infection of the genitourinary tract is uncommon.
- In one literature review, more than 80% of patients with *Cryptococcus* in the urine had disseminated disease, and the mortality rate in this cohort was 64%.

- GU involvement, including pyelonephritis, focal renal abscess, and prostatitis, have been described.
- Systemic antifungal therapy, usually amphotericin B followed by fluconazole, is recommended.

## Fournier Gangrene

### GENERAL CONSIDERATIONS

- Fournier gangrene is a life-threatening necrotizing fasciitis involving the male genitalia. In 1883, the French venereologist Jean Alfred Fournier presented five cases of very rapid, fulminating infection of the genitalia in young male patients.
- The disease now encompasses a broader age range, including older patients, with infection arising from skin, urethral, or rectal sources. Urethral stricture with extravasation, as well as instrumentation or local trauma of the urinary tract, are well-documented factors. An anorectal process such as fistula or abscess can also precipitate the infection. In many cases, no underlying etiologic source is found. Male to female ratio is 10:1.
- Diabetes, alcoholism, malnutrition, and immunosuppression also predispose to Fournier gangrene.
- Erythema occurs as the infection begins with cellulitis of the perineum or scrotum.
- The infection is polymicrobial and includes gram-positive cocci, gram-negative rods, and anaerobic organisms such as *Bacteroides* and *Clostridia*.
- Overall mortality rate of Fournier gangrene is high, approximately 20% in reported series.

### CLINICAL FEATURES AND DIAGNOSIS

- Clinicians should be vigilant and maintain a high index of suspicion for Fournier gangrene in patients who present with significant scrotal discomfort and/or swelling, with fever and systemic toxicity out of proportion to local findings.
- Specific urinary symptoms include dysuria, urethral discharge, and urinary retention.
- Swelling and crepitus of the scrotum and perineum advance rapidly, and tissue becomes dusky as gangrene progresses. A thin, foul-smelling discharge may be present. The process can also spread rapidly to the abdominal wall.

- Urine, tissue, and blood cultures are standard. Radiographic imaging such as KUB or CT may detect soft tissue gas, help assess extent of disease, and detect underlying causes.
- Prompt diagnosis is crucial because the infection is characterized by rapid progression.

## THERAPY

- Urgent assessment and hemodynamic stabilization of the patient, as well as administration of broad-spectrum antibiotics, are required in preparation for surgical debridement.
- Appropriate antibiotic regimens include ampicillin/sulbactam (Unasyn) or a parenteral third-generation cephalosporin, combined with gentamicin. Clindamycin or metronidazole should also be used for anaerobic coverage. Alternatively, imipenem or meropenem can be used as single-agent therapy for polymicrobial infections. Infectious disease consultation is recommended.
- Prompt surgical debridement is essential after the patient is stabilized and antibiotic therapy initiated. Wide excision and debridement of devitalized tissue, as well as extensive skin incisions through involved and adjacent areas, are carried out until normal fascia is found.
- The wounds should be left open (with drains as necessary), and subsequent procedures may be required to reevaluate and further débride tissue of marginal viability.
- Consider urinary diversion with suprapubic cystotomy if there is urethral involvement. A diverting colostomy may be necessary for severe anorectal infection.
- Orchiectomy is rarely required because the separate blood supply to the testicles is not compromised by the infectious process. In many cases, significant excision of devitalized scrotal skin is required, and the defect leaves the gonads exposed (Figure 5-2) If necessary, the testes can be placed in upper medial thigh pouches.
- Hyperbaric oxygen therapy may improve wound healing and shorten the hospital stay.
- Once wound healing is complete, reconstructive techniques (skin grafts, myocutaneous flaps) can be used for improved cosmetic and functional outcomes.

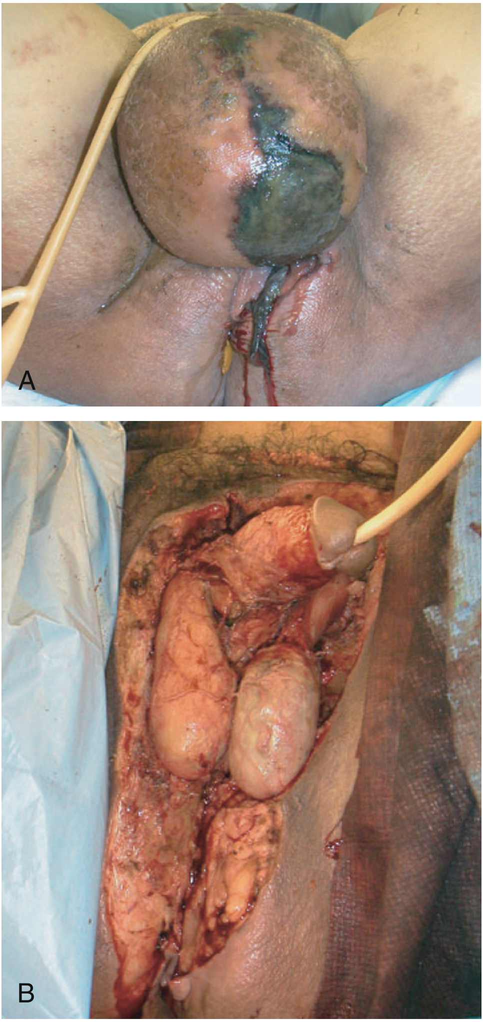

FIGURE 5-2 Fournier gangrene of the scrotum. **A,** Surface appearance of scrotum and perineum showing area of frank necrosis. **B,** Extent of soft tissue debridement required to achieve margins of viable tissue. Note that the testes within their tunica vaginalis compartment are spared. (From Link RE: Cutaneous diseases of the external genitalia. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

## CLINICAL PEARLS

1. Tuberculosis is the most important opportunistic infection in persons infected with HIV, accounting for one fourth of all deaths.
2. The genitourinary tract is the second most common site of extrapulmonary TB; maintain a high index of suspicion in at-risk patients who present with persistent sterile pyuria with or without nonspecific irritative voiding symptoms.
3. Patients with genitourinary bilharzial infection from *Schistosoma hematobium* often present with recurrent secondary bacterial infection from *Salmonella* species.
4. Praziquantel is the medical treatment of choice for all *Schistosoma* infestations; its cure rates are high.
5. Elimination of genital filariasis in endemic areas can be achieved with mass antiinfective therapy and elimination or control of mosquito vectors.
6. Eosinophilia is a common laboratory finding in patients who are diagnosed with a systemic parasitic disease.
7. Initial management of asymptomatic nosocomial fungal colonization of the urinary tract with *Candida albicans* consists of removing antibiotics and indwelling urinary catheters whenever possible; it should also include evaluation of the urinary tract for structural abnormalities or obstruction.
8. Necrotizing fasciitis of the perineum and genitalia (Fournier gangrene) is a life-threatening polymicrobial infection that requires aggressive broad-spectrum antibiotic therapy and prompt surgical intervention for drainage and debridement.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

TABLE 5-E1 **Second-Line Antituberculous Chemotherapeutic Agents**

| | | | |
|---|---|---|---|
| Streptomycin | 15 mg/kg, up to 1 g IM | VIIIth nerve damage (auditory), nephrotoxicity | Audiogram, test vestibular function, BUN/creatinine |
| Amikacin/kanamycin | 15 mg/kg/day, up to 1 g IM | VIIIth nerve damage (auditory), nephrotoxicity | Audiogram, test vestibular function, BUN/creatinine |
| Capreomycin | 12-15 mg/kg, up to 1 g IM daily | VIIIth nerve damage (auditory), nephrotoxicity | Audiogram, test vestibular function, BUN/creatinine |
| Ethionamide | 15 mg/kg, up to 1 g daily, PO | GI disturbance, hepatotoxicity | Monitor LFTs |
| PAS (p-aminosalicylic acid) | 150 mg/kg, up to 12 g daily, PO | GI disturbance, hepatotoxicity | Monitor LFTs |
| Cycloserine | 15 mg/kg, up to 1 g daily, PO | Psychosis, convulsions | Contraindicated in seizure disorder |
| Fluoroquinolones (e.g., ciprofloxacin) | 750-1500 mg daily | GI disturbance, tendinitis | Antacids reduce absorption |
| Rifabutin | 5 mg/kg/day up to 300 mg | Hepatitis, purpura | Orange discoloration |

## Self-Assessment Questions

1. *What laboratory and urine tests are used in the diagnosis of genitourinary tuberculosis (TB)?*
2. *Name an important side effect of isoniazid (INH), and the supplement used to prevent it.*
3. *What is the medical treatment of choice for schistosomal infections?*
4. *Name the four clinical manifestations of filarial disease.*
5. *What are the three most commonly used antifungal agents for treatment of systemic candidiasis?*

## Suggested Readings

1. Centers for Disease Control and Prevention: *Parasites — Lymphatic Filariasis*, www.cdc.gov/parasites/lymphaticfilariasis/.
2. Centers for Disease Control and Prevention: *Parasites — Schistosomiasis*, www.cdc.gov/parasites/schistosomiasis/.
3. Kauffman CA: Candiduria, *Clin Infect Dis* 41:S371–S376, 2005.
4. Kehinde EO, Anim JT, Hira PR: Parasites of urological importance, *Urol Int* 81:1–13, 2008.
5. Pasipanodya J, Hall R II, Gumbo T: Tuberculosis and other mycobacterial diseases. In Bope E, Kellerman R, editors: *Conn's current therapy 2013*, Philadelphia, 2012, Elsevier Saunders, pp 381–386.
6. The Medical Letter: Drugs for tuberculosis, *Treat Guidel Med Letter* 28:83–88, 2004.
7. The Medical Letter: Antifungal drugs, *Treat Guidel Med Letter* 30:7–14, 2005.
8. Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.
9. Wise GJ, Marella VK: Genitourinary manifestations of tuberculosis, *Urol Clin North Am* 30:111–121, 2003.
10. World Health Organization media centre: *Lymphatic filariasis, Fact sheet no. 102*, http://www.who.int/mediacentre/factsheets/fs102/en/.

## CHAPTER 6

# Sexually Transmitted Infections

Edward Zoltan, MD • Ross T. Cockrell, MD

## Introduction

Sexually transmitted infections (STIs) remain a major public health challenge in the United States, affecting more than 20 million men and women annually, nearly half of whom are young people aged 15-24 years. In addition to the physical and psychologic consequences of STIs, these diseases exact a tremendous economic toll. Direct medical costs associated with STIs in the United States are estimated at $16 billion annually treating a total of 110 million STIs.

The curable STIs include gonorrhea, chlamydia, mycoplasma, ureaplasmal infections, syphilis, trichomoniasis, chancroid, lymphogranuloma venereum (LGV), and donovanosis. STIs caused by yeast or protozoa are also curable. Viral STIs include human immunodeficiency virus (HIV), human papillomavirus (HPV), hepatitis B/C virus (HBV, HCV), cytomegalovirus (CMV), and herpes simplex virus (HSV); they are preventable but not curable.

This introduction to STIs is organized and presented by pathogens. A focus on diagnosis and treatment with some epidemiology will be the blueprint for this chapter.

## Bacterial Urethritis

### GONORRHEA

Gonorrhea, *Neisseria gonorrhoeae*, is one of the most commonly reported infectious diseases in the United States, with 321,849 cases reported in 2011. Gonorrhea is thought to be substantially underdiagnosed and underreported; approximately twice as many new infections are estimated to occur each year as are reported.

## Diagnosis

A direct Gram stain may be performed as soon as the specimen is collected. Urethral smears from men who have symptomatic gonorrhea usually contain intracellular gram-negative diplococci in polymorphonuclear leukocytes. Endocervical smears from women and rectal specimens require careful interpretation because of colonization with other gram-negative coccobacillary organisms. In addition, the Centers for Disease Control and Prevention (CDC) is now recommending annual screening for sexually active women with risk factors (i.e., multiple sexual partners, communities with high disease rate). Pregnant women at risk should also receive screening at first prenatal visit. Men who engage in sexual intercourse with other men should be screened more frequently, every 3 to 6 months if illicit drug use is found (especially methamphetamine).

The isolation and identification of *N. gonorrhoeae* is still the currently accepted gold standard for the diagnosis of gonococcal infections. It is the recommended method for medicolegal investigations of sexual abuse. Specimens should be inoculated onto selective media, such as modified Thayer-Martin, Martin-Lewis, or New York City.

Current testing for *N. gonorrhoeae* also includes nucleic acid molecular amplification tests (NAATs) that measure deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) rather than live organisms. Polymerase chain reaction (PCR) (Amplicor, Roche Molecular Diagnostics, Branchburg, N.J.) has been used with sensitivity well above 90% for the detection of *N. gonorrhoeae* in cervical specimens. It is highly accurate with male urine.

Strand displacement amplification (SDA) (ProbeTec, Becton Dickinson, Sparks, Md.) is approved for detection of gonorrhea in cervical, male urethral, and female and male urine samples and has achieved widespread use in clinical laboratories throughout the United States and Europe. The BD ProbeTec ET system demonstrated a sensitivity of 97.9% for the detection of *N. gonorrhoeae* in urine from 680 male patients.

Because NAATs measure DNA or RNA rather than live organisms, caution should be used in using DNA amplification tests for test-of-cure assays. Residual nucleic acid from cells rendered noninfective by antibiotics may give a positive amplified test for up to 3 weeks after therapy, although the patient may actually be cured of viable organisms.

## Treatment of Uncomplicated Gonococcal Urethritis

### *Recommended Regimens*

**Ceftriaxone** 250 mg intramuscularly (IM) in a single dose (99% effective) is the primary choice. If unavailable, **Cefixime** 400 mg orally in a single dose, or **azithromycin** 2 g oral in pregnant women who cannot tolerate cephalosporins *plus, dual therapy to treat chlamydial infection is recommended because treating is more cost effective than testing for associated chlamydial infection:* **azithromycin** 1 g orally in a single dose or **doxycycline** 100 mg orally twice a day for 7 days. Recently two new regimens have been released by the CDC: gentamicin with oral azithromycin (100% effective) and oral azithromycin with oral gemifloxacin (99.5% effective). Given increasing antimicrobial resistance, it is important to consistently consult current literature for updates in treatment. Apps are available from the CDC (www.cdc.gov/mobile/mobileapp.html).

**The CDC no longer recommends quinolones for gonorrhea infections because of new data showing increased resistance.** In addition, use of quinolones is inadvisable for treating infections acquired in California and in other areas with increased prevalence of quinolone resistance.

## Follow-Up

Patients who have uncomplicated gonorrhea and who are treated with any of the recommended regimens need not return for a test to confirm that they are cured. Patients who have symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Infections identified after treatment with one of the recommended regimens usually result from reinfection rather than treatment failure, indicating a need for improved patient education and referral of sex partners. Persistent urethritis, cervicitis, or proctitis may indicate infection by another organism, including *Chlamydia trachomatis*.

All sexual partners who had contact within 60 days of diagnosis should be evaluated, tested, and treated for both *N. gonorrhoeae and C. trachomatis*. Sexual activity should be avoided until treatment is completed and symptoms have resolved in all partners.

## Complications

Complications of *N. gonorrhoeae* may be local or systemic. Locally, male GC urethritis may spread to the posterior urethra, seminal vesicles, and epididymis. This can lead to epididymitis, urethral stricture disease, prostatitis, and even sterility. In women, gonorrhea is a major cause of pelvic inflammatory disease (PID). PID results from the ascent of infection from the endocervix into the fallopian tubes. **Symptoms include vaginal discharge, abdominal pain, dyspareunia, menorrhagia, fever, and cervical motion or adnexal tenderness.** This may lead to scarring of the adnexal structures and fallopian tubes, resulting in chronic pelvic pain, ectopic pregnancy, and infertility.

*N. gonorrhoeae* can also lead to systemic diseases. Gonococcal perihepatitis (Fitz-Hugh-Curtis syndrome) is manifested by sharp supraumbilical pain and right upper quadrant pain. It results from ascending infection from the pelvis into the paracolic gutters and subphrenic spaces in females. “Violin string” adhesions may be noted between the liver and anterior abdominal wall and diaphragm. Disseminated gonococcal infection can occur in up to 3% of mucosal cases and may include arthritis, tenosynovitis, dermatitis, meningitis, myopericarditis, and/or sepsis.

## CHLAMYDIA

Chlamydia, *C. trachomatis*, is the most frequently reported STI in the United States, with an estimated 4 million new cases each year. In 2011, 1.4 million chlamydia diagnoses were reported, up from 877,478 in 2003. National surveys indicate that chlamydia prevalence among sexually active females aged 14 to 19 is 6.8%, Even so, most chlamydia cases go undiagnosed. The increases in reported cases and rates likely reflect the continued expansion of screening efforts and increased use of more sensitive diagnostic tests, rather than an actual increase in new infections. The availability of urine tests for chlamydia may be contributing to the increased detection of the disease in men and consequently the rising rates of reported chlamydia in men in recent years.

**The CDC recommends annual chlamydia screening for sexually active women under age 25, all pregnant women,** and **older women with risk factors (i.e., new or multiple sex partners).** Screening efforts are critical to preventing the serious health consequences of this infection, particularly infertility. Such efforts are linked to a 60% reduction in the incidence of PID. Screening of men who engage in sexual intercourse with other men should be conducted annually, with more frequent screening (every 3 to 6 months) for men involved with multiple partners. If illicit drug use is involved (especially methamphetamine), involved parties are at an even higher risk, and they should receive testing at shorter intervals.

*C. trachomatis* is an intracellular bacterium with multiple serotypes. Types L1-3 cause LGV. Types D, E, F, G, H, I, J, and K cause urethritis and cervicitis. It is transmitted during vaginal, oral, or anal sexual contact with an infected partner. ***C. trachomatis* accounts for 30% to 50% of cases of nongonococcal urethritis (NGU).**

Chlamydial infection in men is generally asymptomatic, but symptoms may include urethritis, epididymitis, and proctitis. Urethritis presents 1 to 3 weeks after infection with a mild to moderate clear urethral discharge and dysuria. Chlamydial urethritis may present as persistent dysuria and/or discharge following a course of treatment for gonorrhea because 15% to 35% of patients with known gonococcal infections are also infected with chlamydia.

Chlamydial epididymitis tends to run a more protracted course than epididymitis because of other organisms; it is also often less severe. Chlamydial proctitis may present with rectal pain and bleeding, but it is often asymptomatic.

Chlamydial infection may disseminate systemically in 1% to 3% of patients. Classically know as Reiter syndrome, it presents with the classic triad of reactive arthritis, urethritis, and conjunctivitis. The Fitz-Hugh-Curtis syndrome may also be seen in about 20% of women with PID secondary to chlamydial infection.

*C. trachomatis* was the first organism for which there was a commercially available PCR assay. Now there are many published studies using several different types of NAATs and new technologies that are commercially available for detecting *chlamydia* in urine and urethral, cervical, or vaginal secretions.

### Treatment

Treatment should be initiated as soon as possible after diagnosis. Single-dose regimens have the advantage of improved compliance.

#### *Recommended Regimens*

- **Azithromycin** 1 g orally in a single dose
- Or **doxycycline** 100 mg orally twice a day for 7 days

#### *Alternative Regimens*

- **Erythromycin base** 500 mg orally four times a day for 7 days
- Or **erythromycin ethylsuccinate** 800 mg orally four times a day for 7 days
- Or **ofloxacin** 300 mg twice a day for 7 days
- Or **levofloxacin** 500 mg once daily for 7 days

## RECURRENT AND PERSISTENT INFECTIONS

Patients who have persistent or recurrent urethritis should be retreated with the initial regimen if they did not comply with the treatment regimen or if they were reexposed to an untreated sex partner. Otherwise, a culture of an intraurethral swab specimen and a first-void urine specimen for *Trichomonas vaginalis* should be performed. Some cases of recurrent urethritis following doxycycline treatment may be caused by tetracycline-resistant *Ureaplasma urealyticum*. If the patient was compliant with the initial regimen and reexposure can be excluded, the following regimen is recommended:

**Metronidazole** 2 g orally in a single dose *PLUS* **erythromycin base** 500 mg orally four times a day for 7 days **or erythromycin ethylsuccinate** 800 mg orally four times a day for 7 days

Patients who have NGU and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

## NONCHLAMYDIAL NONGONOCOCCAL URETHRITIS

The etiologies of most cases of nonchlamydial nongonococcal urethritis are unknown. *U. urealyticum* and *Mycoplasma genitalium* have been implicated. Specific diagnostic tests for these organisms are not indicated because the detection of these organisms is often difficult and would not alter therapy.

*T. vaginalis* and HSV sometimes cause urethritis. Diagnostic and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., contact with trichomoniasis and genital lesions suggestive of genital herpes) or when unresponsive to therapy.

## Genital Lesions

### CONDYLOMA ACUMINATA (GENITAL WARTS)

HPV is the most common STD with an estimated total of 20 million infected individuals in the United States. HPV vaccination has decreased prevalence by 56% in females aged 14 to 19. HPV, a small, nonenveloped virus containing double-stranded DNA, infects basal epithelial cells and multiplies in the cell nucleus, causing cell death and perinuclear cavitation or **koilocytosis, a histologic feature specific to HPV.** More than 40 types of HPV can infect the genital tract. Most HPV infections are asymptomatic, unrecognized, or subclinical. **Visible genital warts usually are caused by HPV type 6 or 11 (90%).** Other HPV types in the anogenital region (e.g., types 16, 18, 31, 33, and 35) have been strongly associated with cervical neoplasia.

Biopsy is recommended under certain clinical conditions:

1. Diagnosis is uncertain.
2. Lesions do not respond to standard therapy.
3. Disease worsens during therapy.
4. Patient is immunocompromised.
5. Warts are pigmented, indurated, fixed, and ulcerated (**suggestive of Buschke-Löwenstein tumor**).

No data support the use of type-specific HPV nucleic acid tests in the routine diagnosis or management of visible genital warts.

In addition to the external genitalia (i.e., the penis, vulva, scrotum, perineum, perianal skin), genital warts can occur on the uterine cervix and in the vagina, urethra, anus, and mouth.

When urethral lesions occur, 80% are located within the distal 3 cm of urethra. Patients present with dysuria, bloody urethral discharge, and changes in urinary stream. **Bladder condyloma are rare.** If meatal condyloma are identified, urethroscopy should be performed to look for other urethral lesions. **To prevent iatrogenic**

**seeding of the prostatic urethra and bladder, a tourniquet should be placed at the penopubic junction, or urethroscopy should stop at the external sphincter.**

Intraanal warts are seen predominantly in patients who have had anal-receptive intercourse; these warts are distinct from perianal warts, which can occur in men and women who do not have a history of anal sex.

HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts. HPV types 6 and 11 rarely are associated with invasive squamous cell carcinoma of the external genitalia. Depending on the size and anatomic location, **genital warts can be painful, friable, and pruritic, although they are commonly asymptomatic.**

HPV types 16, 18, 31, 33, and 35 are found occasionally in visible genital warts and have been associated with external genital (i.e., vulvar, penile, anal) squamous intraepithelial neoplasia (i.e., squamous cell carcinoma in situ, bowenoid papulosis, erythroplasia of Queyrat, Bowen disease of the genitalia). These HPV types also have been associated with vaginal, anal, and cervical intraepithelial dysplasia and squamous cell carcinoma. Patients who have visible genital warts can be infected simultaneously with multiple HPV types (Figure 6-1).

## Treatment

The introduction of two vaccines has resulted in a shift in focus from treatment of visible lesions to prevention: *Cervarix*, a bivalent HPV vaccine against Types 16 and 18 (approximately 70% of cervical cancers) and *Gardasil* a quadrivalent vaccine 16, 18, 6, and 11 (90% of genital warts). Both are administered in three-dose series and are routinely recommended for 11- and 12-year-old girls and boys (Gardasil is the only one FDA approved for boys) and can be started at 9 years of age. Gardasil is also recommended for females 13 to 26 and males 13 to 21 and may be given to 22- to 26-year-old males. Vaccination is also routinely recommended for gay and bisexual men and patients with compromised immune systems (including HIV) aged 22 to 26. Efficacy of the bivalent vaccine in women in preventing cervical cancer related to HPV 16 and 18 is nearly 93% where as the quadrivalent and demonstrated 100% efficacy in preventing cervical, vulvar, and vaginal

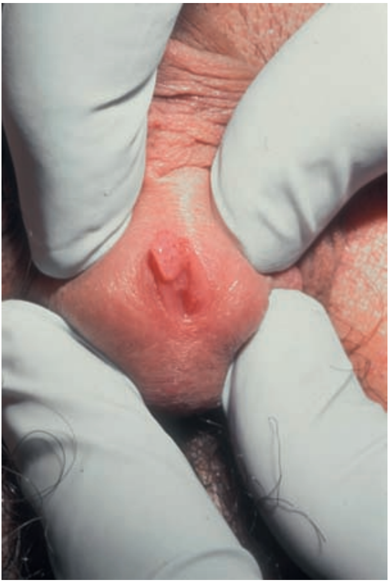

**FIGURE 6-1 Meatal wart caused by human papillomavirus (HPV).** (From Frenkl TL, Potts JM: Sexually transmitted infections. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders, pp 402–416.)

precancers. However, vaccinations do not replace other prevention strategies.

Otherwise, the primary goal of treating visible genital warts is the removal of symptomatic warts. In most patients, treatment can induce wart-free periods. If left untreated, visible genital warts may resolve spontaneously, remain unchanged, or increase in size or number. Existing data indicate that currently available therapies for genital warts may reduce but probably do not eliminate infectivity.

Most patients have fewer than 10 genital warts, with a total wart area of 0.5 to 1.0 $cm^2$. These warts respond to most treatment modalities. Factors that may influence the selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience.

Many patients require a course of therapy rather than a single treatment. In general, warts located on moist surfaces and/or in intertriginous areas respond better to topical treatment than do warts on drier surfaces.

### *Recommended Regimens for External Genital Warts*

**Patient-Applied. Podofilox 0.5% solution or gel:** Patients should apply podofilox solution with a cotton swab or podofilox gel with a finger to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm$^2$, and the total volume of podofilox should be limited to 0.5 mL per day. The safety of podofilox during pregnancy has not been established.

**Imiquimod 5% cream:** Patients should apply imiquimod cream once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after the application. The safety of imiquimod during pregnancy has not been established.

**Sinecatechins 15% ointment**: Patients should apply the ointment three times daily for up to 16 weeks. DO NOT wash off postapplication. The safety of sinecatechins during pregnancy or in HIV or HSV–co-infection has not been established.

**Physician-Administered. Cryotherapy** with liquid nitrogen or cryoprobe: Repeat applications every 1 to 2 weeks.

**Podophyllin resin 10% to 25%** in a compound tincture of benzoin: A small amount should be applied to each wart and allowed to air dry. The treatment can be repeated weekly if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, the application should be limited to less than 0.5 mL of podophyllin or an area of less than 10 cm$^2$ of warts per session. The preparation should be thoroughly washed off 1 to 4 hours after application to reduce local irritation. The safety of podophyllin during pregnancy has not been established.

**Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80% to 90%:** A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate (i.e., baking soda), or liquid-soap preparations to remove unreacted acid. This treatment can be repeated weekly if necessary.

### *Surgical Removal for Very Large Wart Burden*

**Intralesional interferon:** Intralesional injection of interferon alpha 2b increases success of podofilox, but the recurrence rate is the same.

**Laser surgery:** Carbon dioxide ($CO_2$) laser vaporizes tissue with a shallow depth of penetration. **Must use laser mask and vacuum because viral DNA has been demonstrated in the smoke plume.** Neodymium:yttrium-aluminum-garnet (Nd:YAG) coagulates tissue and causes less plume. Overall success with laser is 88% to 100%. Recurrence may occur in 2 to 3 months.

## GENITAL ULCERS

In the United States, most young, sexually active patients who have genital ulcers have genital herpes, syphilis, or chancroid. Although genital herpes is the most prevalent of these diseases, the relative frequency of each differs by geographic area and patient population. Patients with genital ulcers may have more than one disease. Conversely, not all genital ulcers are caused by STIs. Each disease has been associated with an increased risk for HIV infection.

A diagnosis based only on the patient's medical history and physical examination often is inaccurate.

Only three ulcer presentations are pathognomonic:

1. A fixed drug eruption is always triggered by the use of one particular medication.
2. A group of vesicles on an erythematous base that does not follow a neural distribution is pathognomonic for herpes simplex infection.
3. A genital ulcer that develops acutely following sexual activity is diagnostic of trauma.

Specific tests for evaluation of genital ulcers include:

1. Serology and either darkfield examination or direct immunofluorescence test for *Treponema pallidum*
2. Culture or antigen test for HSV
3. Culture for *Haemophilus ducreyi* (chancroid)

The differential diagnosis of genital ulcers must include premalignant processes (e.g., erythroplasia of Queyrat); malignant processes such as squamous cell carcinoma of the penis; and

TABLE 6-1 **Genital Ulcer Disease**

| Disease | Lesions | Lymphadenopathy | Systemic Symptoms |
|---|---|---|---|
| Primary syphilis | Painless, indurated, with a clean base, usually singular | Nontender, rubbery, nonsuppurative bilateral lymphadenopathy | None |
| Genital herpes | Painful vesicles, shallow, usually multiple | Tender, bilateral inguinal adenopathy | Present during primary infection |
| Chancroid | Tender papule, then painful, undermined purulent ulcer, single or multiple | Tender, regional, painful, suppurative nodes | None |
| Lymphogranuloma | Small, painless vesicle or papule progresses to an ulcer | Painful, matted, large nodes develop, with fistulous tracts | Present after genital lesion heals |

*(From Frenkl TL, Potts JM: Sexually transmitted infections. In Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 10, Philadelphia, 2012, Saunders, pp 402–416.)*

nonmalignant processes, including syphilis, chancroid, LGV, and granuloma inguinale (GI). Biopsy of ulcers may be helpful in identifying the cause of unusual ulcers or ulcers that do not respond to initial therapy (Table 6-1).

## Genital Herpes

Genital herpes is a recurrent, life-long viral infection. Two serotypes of HSV have been identified: HSV-1 (30%) and HSV-2 (70%). Most cases of recurrent genital herpes are caused by

HSV-2, although an increasing number of HSV-1 anogenital cases are being seen. Approximately 24 million persons in the United States have a genital HSV-2 infection, and most are undiagnosed; in addition, 776,000 new cases are reported each year.

Herpes virus invades the body via breaks in the skin or moist membranes of the penis, vagina, urethra, anus, vulva, or cervix. **Genital lesions appear 2 to 20 days after infection.** The lesions are initially papules, which ulcerate and scab before reepithelializing. Flulike symptoms may develop with the initial infection and are much worse than subsequent episodes or in patients without history of previous oral herpes. Local lesions may persist an average of 10 days following the initial infection. Recurrent lesions last 5 to 7 days. Tender inguinal adenopathy can develop in 2 to 3 weeks. Dysuria is present in 80% of females and 40% of males with genital herpes.

Late complications include mild meningitis (10% to 30%) and sacral or autonomic dysfunction (1%), which can result in urinary retention, pneumonitis, and hepatitis. The most serious consequence is neonatal transmission, which carries high rates of morbidity and mortality for the infant.

All types of intercourse may transmit HSV, and HSV may be passed on to the baby during birth. Most genital herpes infections are transmitted by persons who are either unaware of their status or asymptomatic. Rarely does first-episode genital herpes manifest with severe disease requiring hospitalization.

**Recurrences are much less frequent for genital HSV-1 infection than genital HSV-2 infection**. Making the distinction between HSV serotypes is important in prognosis and counseling. As such, the clinical diagnosis of genital herpes should be confirmed by laboratory testing.

Cell culturing and type analysis by immunofluorescence tests are standard options for diagnosis. Fluorescence tests can be done without viral amplification in the cell culture but with decreased sensitivity. PCR and ligase chain reaction (LCR) amplification of HSV show much better sensitivity, but the techniques are too expensive for routine use. Cytologic detection of cellular changes of herpes virus infection is insensitive and nonspecific, both in genital lesions (Tzanck preparation) and cervical Pap smears, and should not be relied on for diagnosis of HSV infection. Alternatively for serum HSV2 antibody, glycoprotein G type are available and have a specificity of greater than 96% (Figure 6-2).

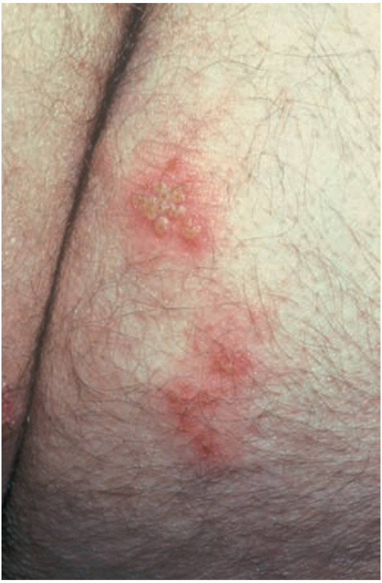

**FIGURE 6-2 Typical vesicular eruption of herpes simplex virus (HSV).** (From Frenkl TL, Potts JM: Sexually transmitted infections. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders, pp 402–416.)

## TREATMENT

Systemic antiviral drugs partially control the symptoms and signs of herpes episodes when used to treat first clinical episodes and recurrent episodes or when used as daily suppressive therapy. Nonetheless, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued.

Randomized trials indicate that **three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir.** Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir, a prodrug of penciclovir, also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit.

### First Clinical Episode of Genital Herpes

Many patients with first-episode herpes present with mild clinical manifestations. Most first episodes go unnoticed, but later patients can develop severe or prolonged symptoms. Therefore most patients with initial genital herpes should receive antiviral therapy.

*Recommended Regimens*

- **Acyclovir** 400 mg orally three times a day for 7 to 10 days
- Or **acyclovir** 200 mg orally five times a day for 7 to 10 days
- Or **famciclovir** 250 mg orally three times a day for 7 to 10 days
- Or **valacyclovir** 1 g orally twice a day for 7 to 10 days

## Episodic Therapy for Recurrent Genital Herpes

Effective episodic treatment of recurrent herpes requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of the drug or a prescription for the medication with instructions to self-initiate treatment immediately when symptoms begin.

*Recommended Regimens*

- **Acyclovir** 400 mg orally three times a day for 5 days
- Or **acyclovir** 200 mg orally five times a day for 5 days
- Or **acyclovir** 800 mg orally twice a day for 5 days
- Or **famciclovir** 125 mg orally twice a day for 5 days
- Or **valacyclovir** 500 mg orally twice a day for 3 to 5 days
- Or **valacyclovir** 1.0 g orally once a day for 5 days

## Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy reduces the frequency of genital herpes recurrences by 70% to 80% among patients who have frequent recurrences (i.e., six recurrences per year), and many patients report no symptomatic outbreaks.

The frequency of recurrent outbreaks diminishes over time. Periodically (e.g., once a year), discontinuation of therapy should be discussed with the patient to reassess the need for continued therapy.

Suppressive antiviral therapy reduces but does not eliminate subclinical viral shedding. Therefore the extent to which suppressive therapy prevents HSV transmission is unknown.

*Recommended Regimens*

- **Acyclovir** 400 mg orally twice a day
- Or **famciclovir** 250 mg orally twice a day

- Or **valacyclovir** 500 mg orally once a day
- Or **valacyclovir** 1.0 g orally once a day

### Severe Disease

Intravenous (IV) acyclovir therapy should be provided for patients who have severe disease or complications that necessitate hospitalization, such as disseminated infection, pneumonitis, hepatitis, or complications of the central nervous system (e.g., meningitis, encephalitis). The recommended regimen is acyclovir 5 to 10 mg/kg of body weight IV every 8 hours for 2 to 7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.

### Pregnancy and HSV

Given the high vertical transmission rates (30% to 50%) for HSV to newborns during vaginal delivery, all expectant mothers should be evaluated for infections or history of infections. Direct exposure is required for transmission; therefore avoidance of exposure during delivery is the focus of prevention. Cesarean delivery is recommended in the face of active or ongoing infection, thus preventing exposure and decreasing likely transmission at the time of delivery. Acyclovir oral or IV can be administered late in pregnancy and has been documented to decrease the need for cesarean sections. If the neonate is exposed, systemic acyclovir should be administered.

## Syphilis

Syphilis is a systemic disease caused by *Treponema pallidum,* a spirochete bacterium. Patients who have syphilis may seek treatment for signs or symptoms of primary infection, secondary infection, or tertiary infection.

The ulcer in primary syphilis is characteristically **firm, hard (because of endarteritis and vascular sclerosis), and painless.** In men, the most common area is on the corona of the penis. In women, the most common locations are the labia majora, labia minora, fourchette, and perineum.

The primary mode of transmission is sexual contact. Ten percent of cases are due to transmission via saliva, transfusions, and accidental inoculation. **The disease is most contagious during the**

**secondary stage because of the increased number of lesions present.** The risk of transmission exists during all stages, except latent syphilis.

## PRIMARY SYPHILIS

The time from transmission to the appearance of primary lesions averages 21 days (the range is 10 to 90 days). The clinical presentation of syphilis is extremely diverse and may occur decades after initial infection.

The primary chancre appears at the site of initial treponemal invasion of the dermis. It may occur on any skin or mucous membrane surface and is usually situated on the external genitalia. Initial lesions are papular but rapidly ulcerate. They are usually single, but "kissing" lesions may occur on opposing mucocutaneous surfaces. Typically, the ulcers are nontender (unless there is coexisting infection) and indurated and have a clean base and raised edges. There is often surrounding edema, especially with vulval lesions. Nontender, nonsuppurative, rubbery inguinal lymphadenopathy appears 1 week later and usually becomes bilateral after 2 weeks. The chancre usually heals spontaneously within 3 to 6 weeks but leaves a scar (Figure 6-3).

## SECONDARY SYPHILIS

The manifestations of generalized treponemal dissemination first appear about 8 weeks after infection. Constitutional symptoms consist of fever, headache, and bone and joint pains. Physical features are widely diverse. Skin rashes are the most common feature. They are initially macular and become papular by 3 months. Lesions appear initially on the upper trunk, the palms and soles, and flexural surfaces of the extremities.

Generalized lymphadenopathy occurs in 50% of cases of secondary syphilis. It has similar characteristics to the localized lymphadenopathy of primary infection. Other systemic features of secondary syphilis include panuveitis, periostitis and joint effusions, glomerulonephritis, hepatitis, gastritis, myocarditis, and aseptic meningitis.

The lesions of secondary syphilis resolve spontaneously in a variable time period and most patients enter the latency stage within the first year of infection. In some patients, especially the immunocompromised, primary or secondary lesions may recur.

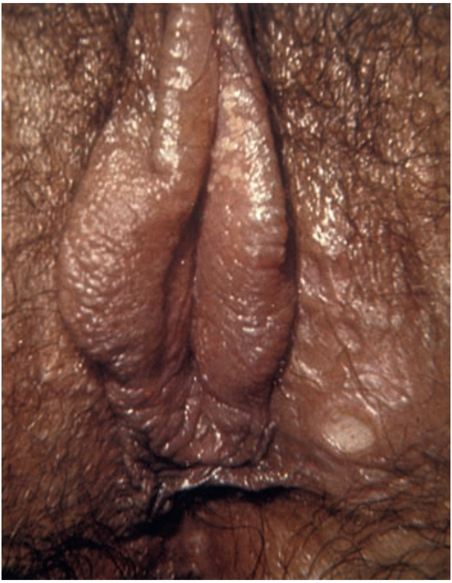

FIGURE 6-3 **Syphilis with vulvar chancre.** (From Frenkl TL, Potts JM: Sexually transmitted infections. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders, pp 402–416.)

## LATENT SYPHILIS

In latent syphilis, no clinical stigmata of active disease is visible, although the disease remains detectable by positive serologic tests. In early latency, within 2 years of infection, vertical transmission of infection may still occur, but sexual transmission is less likely in the absence of mucocutaneous lesions. The late manifestations of syphilis arise, often decades later, in about 25% of those who have latent syphilis.

## TERTIARY GUMMATOUS SYPHILIS

The characteristic lesions of tertiary syphilis appear 3 to 10 years after infection and consist of granulomas or gummas. The granulomas appear as cutaneous plaques or nodules of irregular shape and outline and are often single lesions on the arms, back, and face. Gummas can cause painless testicular swelling, which may mimic a tumor. The typical lesion of cardiovascular syphilis is aortitis affecting the ascending aorta and appearing 10 to 30 years after infection. This can result in aortic aneurysms or aortic insufficiency. Symptoms of neurosyphilis include dementia, sensory ataxia, areflexia, paresthesias, auditory abnormalities, and Argyll Robertson pupils (pupils that have accommodation but no pupil response).

## DIAGNOSIS

Dark-field examinations and direct fluorescent antibody tests of lesion exudate or tissue are the definitive methods for diagnosing early syphilis. A presumptive diagnosis is possible with the use of two types of serologic tests for syphilis: (1) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) and (2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] and *T. pallidum* particle agglutination [TP-PA]). The use of only one type of serologic test is insufficient for diagnosis because false-positive nontreponemal test results may occur secondary to various medical conditions.

Nontreponemal test antibody titers usually correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Nontreponemal tests usually become nonreactive with time after treatment; however, in some patients, nontreponemal antibodies can persist at a low titer for a long period of time, sometimes for the life of the patient. This response is referred to as the *serofast reaction*.

## TREATMENT

**Penicillin G, administered parenterally, is the preferred drug for treatment of all stages of syphilis.** The preparation(s) used (i.e., benzathine, aqueous procaine, aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of disease. However, neither combinations of benzathine penicillin and procaine penicillin nor oral penicillin preparations are considered appropriate for the treatment of syphilis.

**Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy.** Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin. Skin testing for penicillin allergy may be useful in pregnant women; such testing also is useful in other patients.

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, and other symptoms that usually occurs within the first 24 hours after any therapy for syphilis. Patients should be informed about this possible adverse reaction. **It occurs most often among patients who have early syphilis.** Antipyretics may be used, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress in pregnant women. This concern should not prevent or delay therapy.

### Primary and Secondary Syphilis

#### *Recommended Regimen for Adults*

**Benzathine penicillin G** 2.4 million units IM in a single dose

Patients with penicillin allergy can be treated with doxycycline (100 mg orally twice daily for 14 days), tetracycline (500 mg four times daily for 14 days), ceftriaxone 1 g daily IM or IV for 8 to 10 days, or azithromycin as a single oral dose of 2 g. **Patients whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin.**

## Chancroid

Chancroid is a bacterial disease caused by *Haemophilus ducreyi,* a gram-negative rod, which is transmitted by direct sexual contact. In the United States, chancroid usually occurs in discrete outbreaks, although the disease is endemic in some areas. Chancroid is a cofactor for HIV transmission; high rates of HIV infection occur among patients who have chancroid in the United States and other countries.

An erythematous papule develops where the bacteria entered the body 3 to 14 days after contact. The pustule breaks down into the classic dirty, painful, nonindurated ulcer. Fifty percent of patients will have tender inguinal adenopathy, with matting of nodes. The lymph nodes in the groin are filled with pus (buboes).

The combination of a painful ulcer and tender inguinal adenopathy, symptoms occurring in one third of patients, suggests a diagnosis of chancroid; when accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.

### DIAGNOSIS

A definitive diagnosis of chancroid requires identification of *H. ducreyi* on special culture media (supplemented gonococcal base and Mueller-Hinton agar) that is not widely available from commercial sources; even when using these media, sensitivity is 80%. No Food and Drug Administration (FDA)-approved PCR test for *H. ducreyi* is available in the United States.

### TREATMENT

Successful treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, scarring can result despite successful therapy. Resistance to various antibiotics has been a problem in the treatment of chancroid because of plasmid-mediated phenomenon. Those populations with HIV or uncircumcised men will generally not respond to treatment as well as comparative populations (Figure 6-4).

#### Recommended Regimens

- **Azithromycin** 1 g orally in a single dose
- Or **ceftriaxone** 250 mg IM in a single dose
- Or **ciprofloxacin** 500 mg orally twice a day for 3 days
- Or **erythromycin** base 500 mg orally three times a day for 7 days

## Lymphogranulum Venereum

LGV is caused by *C. trachomatis* subtype L1, L2, or L3. The disease occurs most commonly in tropical climates and rarely in the United States. The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is most commonly unilateral. Women and homosexually active men may have proctocolitis or inflammatory involvement of perirectal or perianal lymphatic tissues resulting

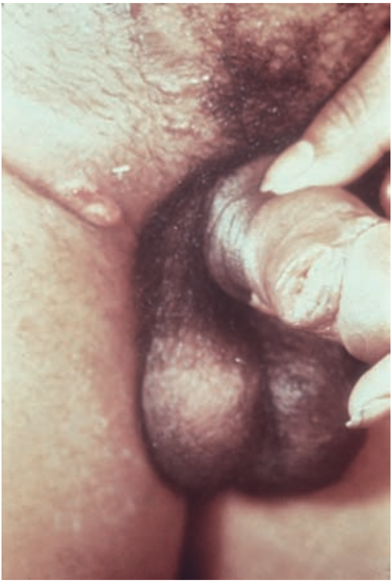

**FIGURE 6-4 Chancroid with regional adenopathy.** (From Frenkl TL, Potts JM: Sexually transmitted infections. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders, pp 402–416.)

in fistulas and strictures, tertiary LGV. A self-limited genital ulcer sometimes occurs at the site of inoculation. The lymphadenopathy occurs 2 to 6 weeks after inoculation. However, by the time patients seek care, the ulcer usually has disappeared (conversely, patients with chancroid have the ulcer and lymphadenopathy concomitantly.)

The diagnosis of LGV is based on clinical suspicion and usually made serologically and by exclusion of other causes of inguinal lymphadenopathy or genital ulcers. Chlamydiae have to be cultured in special cell cultures (McCoy cells) and can be diagnosed by fluorescence antibody tests. Complement fixation titers 1:64 are consistent with the diagnosis of LGV.

Treatment cures infection and prevents ongoing tissue damage. Aspiration or incision and drainage to prevent formation of inguinal or femoral ulcerations in addition to an appropriate antibiotic regimen may be required.

### RECOMMENDED REGIMEN

- **Doxycycline** 100 mg orally twice a day for 21 days
- Or **erythromycin** base 500 mg orally four times a day for 21 days

Pregnant and lactating women should be treated with erythromycin. Azithromycin may prove useful for treatment of LGV in pregnancy, but no published data are available regarding its safety and efficacy. Doxycycline is contraindicated in pregnant women.

## Granuloma Inguinale

GI, also known as *donovaniasis*, is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (previously *Calymmatobacterium granulomatis*). The organism is found in vacuolated inclusions within leukocytes known as ***Donovan bodies*.**

The disease occurs rarely in the United States, although it is endemic in certain tropical and developing areas, including India; Papua, New Guinea; central Australia; and southern Africa. Clinically, the disease commonly presents as painless, progressive ulcerative lesions **without regional lymphadenopathy.** The lesions appear 8 days to 12 weeks after inoculation. They are highly vascular ("beefy red appearance") and bleed easily on contact. However, the clinical presentation can also include hypertrophic, necrotic, or sclerotic variants.

GI is generally diagnosed by visual observation of the external symptoms. Gram-stained samples will show the bacteria, which can be cultured under special conditions only. Donovan bodies are found in macrophages on tissue crush preparation or biopsy.

### TREATMENT

Treatment halts progression of lesions, although prolonged therapy may be required to permit granulation and reepithelialization of the ulcers. Relapse can occur 6 to 18 months after apparently effective therapy.

#### Recommended Regimens

- **Doxycycline** 100 mg orally twice a day for at least 3 weeks
- Or **trimethoprim-sulfamethoxazole** one double-strength (800 mg/160 mg) tablet orally twice a day for at least 3 weeks

### Alternative Regimens

- **Ciprofloxacin** 750 mg orally twice a day for at least 3 weeks
- Or **erythromycin base** 500 mg orally four times a day for at least 3 weeks
- Or **azithromycin** 1 g orally once per week for at least 3 weeks

Gentamicin (1 mg/kg IV every 8 hours) can be used if lesions do not respond to initial oral therapy in several days or if the patient is HIV positive.

## Mollusca Contagiosum

Mollusca contagiosum is a benign dermatologic disease caused by the mollusca contagiosum virus (poxivirdae family); it has a sexual mode of transmission. MCV may be transmitted by skin-to-skin contact, fomites, or self-innoculation.

The incubation period is 2 to 7 weeks. The lesions caused by MCV typically appear as flesh-colored, pearly pink, umbilicated, raised papules (1 to 5 mm in diameter) or nodules (6 to 10 mm), which may be single or multiple. Patients are often asymptomatic.

The diagnosis can be confirmed by light microscopy or electron microscopy of biopsies taken from a blister. Biopsy shows molluscum body, cytoplasmic inclusions containing viral particles. These intracytoplasmic inclusions are also known as Henderson-Paterson bodies and are pathognomonic.

### TREATMENT

Blisters will regress spontaneously under the control of the immune system. If not, surgical removal by laser, cryotherapy, electrosurgery, or chemical treatment is recommended.

## Vaginitis

Vaginal infection is usually characterized by a vaginal discharge or vulvar itching and irritation; a vaginal odor may be present. The three diseases most frequently associated with vaginal discharge are trichomoniasis (caused by *T. vaginalis*), bacterial vaginosis (BV; caused by a replacement of the normal vaginal flora by an overgrowth of anaerobic microorganisms, mycoplasmas, and *Gardnerella vaginalis*), and candidiasis (usually caused by *Candida albicans*). These infections are often diagnosed in women being evaluated for STIs.

The cause of vaginal infection can be diagnosed by pH and microscopic examination of the discharge. The pH of the vaginal secretions can be determined by narrow-range pH paper for the elevated **pH (greater than 4.5) typical of BV or trichomoniasis.** Discharge can be examined by diluting one sample in one to two drops of 0.9% normal saline solution on one slide and a second sample in 10% potassium hydroxide (KOH) solution. **An amine odor detected before or immediately after applying KOH suggests BV.** The motile *T. vaginalis* or the clue cells of BV usually are identified easily in the saline specimen. The yeast or pseudohyphae of *Candida* species are more easily identified in the KOH specimen.

## BACTERIAL VAGINOSIS

BV is a clinical syndrome resulting from replacement of the normal $H_2O_2$-producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (e.g., *Prevotella* sp., *Mobiluncus* sp.), G*ardnerella vaginalis,* and *Mycoplasma hominis*. BV is the most prevalent cause of vaginal discharge or malodor; however, up to 50% of women with BV may not report symptoms of BV. BV is associated with having multiple sex partners, douching, and lack of vaginal lactobacilli; it is unclear whether BV results from acquisition of a sexually transmitted pathogen. Women who have never been sexually active are rarely affected. Treatment of the male sex partner has not been beneficial in preventing the recurrence of BV.

BV can be diagnosed by the use of clinical or Gram stain criteria. Clinical criteria require three of the following symptoms or signs:

1. A homogenous, white, noninflammatory discharge that smoothly coats the vaginal walls
2. The presence of clue cells on microscopic examination
3. A pH of vaginal fluid greater than 4.5
4. A fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test)

### Recommended Regimens

- **Metronidazole** 500 mg orally twice a day for 7 days
- Or **metronidazole gel** 0.75%, one full applicator (5 gm) intravaginally once a day for 5 days
- Or **clindamycin** cream 2%, one full applicator (5 gm) intravaginally at bedtime for 7 days

## TRICHOMONIASIS

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Most men who are infected with *T. vaginalis* do not have symptoms. Many infected women present with symptoms characterized by a diffuse, malodorous, yellow-green discharge with vulvar irritation and will typically report similar high-risk behaviors: multiple sex partners, history of STIs, exchange money for sex, use IV drugs. However, some women have minimal or no symptoms. Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions.

Culture is the most sensitive, commercially available method of diagnosis. No FDA-approved PCR test for *T. vaginalis* is available in the United States.

### Recommended Regimens

Metronidazole 2 gm orally in a single dose

## VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC) usually is caused by *C. albicans* but occasionally is caused by other *Candida* sp. or yeasts. Typical symptoms of VVC include pruritus and vaginal discharge. Other symptoms include vaginal soreness, vulvar burning, dyspareunia, and external dysuria. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40% to 45% will have two or more episodes.

### Treatment

Short-course topical formulations (i.e., single dose, regimens of 1 to 3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80% to 90% of patients who complete therapy.

## Ectoparasites

### PHTHIRUS PUBIS

*Phthirus pubis* is a tiny insect that infects the pubic hair of its victims and feeds on human blood. They use crablike claws to grasp the hair of their host and can crawl several centimeters per day. Female lice lay two to three eggs daily and affix them to the hairs (nits). During direct sexual contact, the insects can move from one partner to the other. **Itching in the pubic area is a telltale sign.** Microscopic examination of the lice or the nits can confirm this.

Treatment involves applying Permethrin or Pyrethrins to affected areas and washing off after 10 minutes. The scalp is treated with lindane 1% shampoo applied for 4 minutes and then washed off. Patients with pediculosis pubis should be evaluated for other STIs.

## Human Immunodeficiency Virus

HIV is an RNA virus (retrovirus) that binds to the CD4 molecule on T4 lymphocytes and some other cell types. Viral RNA undergoes reverse transcription to DNA, which is incorporated into the host DNA. Viral replication occurs by transcription of proviral DNA into viral mRNA, which is associated with a decline in the CD4 cell count and defeat of the immune system. HIV has been isolated from blood, semen, vaginal secretions, saliva, tears, urine, amniotic fluid, breast milk, and cerebrospinal fluid. However, **evidence has implicated only blood, semen, and vaginal secretions in the transmission of the virus.**

Both viral load (molecules of viral RNA/mL) and CD4 T-cell count are used to monitor and prognosticate disease progression to acquired immunodeficiency syndrome (AIDS). **CD4 counts of fewer than 500 cells/μL are associated with a greater risk of opportunistic infections and progression to AIDS; below 200 cells/μL are at high risk for life-threatening opportunistic infections.**

Diagnostic tests for HIV include measurement of anti-HIV antibodies using an enzyme-linked immunosorbent assay (ELISA); antibody-positive specimens are tested using the Western blot assay, which is more specific. Antibodies can be detected on day 21 after initial exposure. Also, after acute infection, HIV RNA can be detected from day 12 through RNA assays. This testing is used in treatment by evaluation of viral load as a response to current therapy.

Treatments include nucleoside analogue reverse-transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. Indinavir and nelfinavir are associated with renal stones in up to 4% of cases. These stones are not visualized on x-ray or computed tomography. Patients usually improve with hydration and discontinuation of the drug. If necessary, ureteral stenting will usually suffice.

Of concern now with expanding antiviral medication is development of drug resistance. Recommendations include directed viral testing prior to initiation of antiviral therapy.

## EPIDEMIOLOGY

According to World Health Organization (WHO) estimates, 34 million people worldwide were infected with HIV in December 2011; more than 80% occurred through sexual intercourse. An estimated 70% of HIV-positive men acquired the virus through vaginal intercourse. HIV is more likely in people who have had STDs, especially genital ulcer disease.

Individuals who are infected with STDs are at least two to five times more likely than uninfected individuals to acquire HIV if they are exposed to the virus through sexual contact. In addition, if an HIV-infected individual is also infected with another STD, that person is more likely to transmit HIV through sexual contact than other HIV-infected persons.

STDs probably increase susceptibility to HIV infection by two mechanisms. Genital ulcers (e.g., syphilis, herpes, chancroid) result in breaks in the genital tract lining or skin. These breaks create a portal of entry for HIV. Nonulcerative STDs (e.g., chlamydia, gonorrhea, trichomoniasis) increase the concentration of cells in genital secretions that can serve as targets for HIV (e.g., CD4+ cells).

Studies have shown that when HIV-infected individuals are also infected with other STDs, they are more likely to have HIV in their genital secretions. For example, men who are infected with both gonorrhea and HIV are more than twice as likely to shed HIV in their genital secretions as those who are infected only with HIV. Moreover, the median concentration of HIV in semen is as much as 10 times higher in men who are infected with both gonorrhea and HIV than in men infected only with HIV.

In the HIV-positive patient, genital ulcers are usually caused by STDs such as genital herpes, syphilis, and chancroid, but they may also be part of a systemic illness such as herpes zoster or CMV or may be related to drug therapy (e.g., with the antiviral agent foscarnet).

Serologic tests for syphilis may be false negative in the HIV-infected patient, with a tendency to delayed appearance of seroreactivity. HIV patients with syphilis are more likely to encounter neurologic complications and have a higher rate of treatment failure. Condyloma acuminatum is very common in HIV-infected patients. Visible genital warts caused by HPV type 6 or 11 are found in 20% of HIV-infected patients, compared with 0.1% of the general population.

Molluscum contagiosum (MCV) infection occurs in 5% to 18% of HIV-positive patients. HIV-positive patients tend to develop giant (greater than 1 cm) lesions or may have clustering of hundreds of small lesions and are at greater risk for secondary inflammation and bacterial infection. MCV lesions in patients with HIV do not resolve quickly, are spread easily to other locations, and are refractory to common treatments. Differential diagnosis includes condylomata acuminata for small, and squamous carcinoma for large, solitary lesions. Treatment options for MCV are the same as for genital warts.

Additionally, recent studies support the conclusion that circumcised men are at a lower risk for HIV infections. A movement for adult circumcisions has been initiated in HIV-laden populations because this is one of a few proven prevention strategies.

## MALIGNANCIES

**Kaposi sarcoma (KS)** is a sarcoma of endothelial origin affecting the feet and lower extremities and (rarely) the genitalia. Prior to 1981 it was seen only in elderly men of Mediterranean descent and ran an indolent course (now called “classic” Kaposi sarcoma). Development of KS in the HIV population is from a KS-associated herpes virus that is sexually transmitted. Twenty percent of patients with HIV-associated KS will develop lesions on the genitalia. Lesions are subcutaneous, nonpruritic nodules. They can be pigmented, sometimes appearing blue. Lymphedema is common.

Treatment includes local excision, laser fulguration, or radiation therapy for the small solitary lesion. Larger lesions are treated with radiation therapy with possible side effects of urethral strictures or fistulae. Disseminated KS is treated with chemotherapy and interferon.

Testicular tumors occur in up to 0.2%, or 50 times that of the general population. Seminomatous and nonseminomatous tumors are seen, along with HIV-related non-Hodgkin lymphoma involving the testes. Testicular lymphoma in HIV patients presents in younger men and with higher grade tumor than in non-HIV men.

Treatment for these tumors follow the standard treatment guidelines if the patient can tolerate the therapy.

Renal, penile, and cervical cancers are also more common in HIV patients and adopt more aggressive courses.

## IMPOTENCE

Erectile and ejaculatory dysfunction are common problems in HIV-infected men. It is estimated that 67% and 33% of men with AIDS have decreased libido and impotence, respectively. Typically, these HIV-positive men have low serum testosterone levels, normal luteinizing hormone (LH) but high follicle-stimulating hormone (FSH) levels, and oligoteratospermia. Testicular atrophy results from the direct cytotoxic effect of HIV on the germinal and Sertoli cells and secondary effects of HIV infection, such as opportunistic infection of the testes, side effects from medication, and effects of cytokines on the hypothalamic-pituitary-gonadal axis.

They may also suffer from psychologic depression, AIDS-related dementia, and neurogenic dysfunction, including peripheral neuropathy from viral myelitis and myelopathy, which occurs in 30% to 40% of AIDS patients. **Patients can be treated successfully with testosterone supplements, phosphodiesterase-5 (PDE-5) inhibitors, or intracavernosal/intraurethral prostaglandins.**

## VOIDING DYSFUNCTION

Impaired micturition becomes more common with disease progression and can occur as part of an overall neurologic dysfunction or through infection. In a series of 39 HIV-positive patients presenting with lower urinary tract symptoms (LUTS) and undergoing urodynamics, a urodynamic abnormality (overactive or underactive detrusor or detrusor sphincter dyssynergia) was identified in 87% of patients. Of these, 61% had AIDS-related neurologic problems, such as cerebral toxoplasmosis, HIV demyelination disorders, and AIDS-related dementia. This heralded a poor prognosis because 43% in this group died after 2 to 24 months (mean 8). Detrusor failure caused by lower motor injury is uncommon and is usually ascribed to malignancy or infection such as herpes. Patients should be taught clean intermittent catheterization (CIC); long-term indwelling catheters are best avoided in HIV-infected patients because of their vulnerability to *Staphylococcus aureus* bacterium.

## CLINICAL PEARLS

1. Given the growing rate of microbial resistance to common antibiotics, the Centers for Disease Control (CDC) or similar authoritative sources should be periodically consulted for up-to-date therapeutic recommendations.
2. Treatment and education of not only the presenting patient but also his or her sexual partners is key in treating sexually transmitted infections (STIs) and controlling their spread.
3. Given the asymptomatology of many STIs, screening is key in diagnosing and controlling infections within respective at-risk patient populations.
4. An iPad app about STI is available from the CDC (http://www.cdc.gov/std/std-tx-app.htm).

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What is the histologic feature specific to granuloma inguinale?*
2. *Which antibiotics can be used in pregnancy?*
3. *What is the most common cause of genital ulcers in the United States?*
4. *A 35-year-old man presents with tender unilateral inguinal adenopathy. There is some suppuration of the nodes along with the spread to involve the rectum. He does not recall having a genital lesion at any time. What is the most likely diagnosis?*
5. *A sexually active 25-year-old woman presents with a 3-day history of dysuria and vaginal discharge. The pH of the discharge is 4.5. There is no amine odor on addition of 10% KOH to the discharge (i.e., a negative whiff test). On microscopy, there are numerous polymorphonuclear leukocytes (PMNs) and no clue cells. What is the most likely diagnosis?*
6. *What are the recommendations for HPV vaccination for females? For males? What are the two available, FDA-approved vaccinations?*

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# CHAPTER 7

# Interstitial Cystitis/Bladder Pain Syndrome

Philip M. Hanno, MD, MPH

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a condition diagnosed primarily on the basis of clinical symptomatology. It requires a high index of suspicion on the part of the healthcare provider. It should be considered in the differential diagnosis of the patient presenting with chronic pelvic pain, often exacerbated by bladder filling and associated with urinary frequency. **The *sine qua non* of the diagnosis is the presence of pain associated with the bladder.** The older term *interstitial cystitis* (or *IC*) was not at all descriptive of the clinical syndrome and not accurate with regard to the pathologic findings. The reader should realize that the older term is still in use and common in the literature but gradually becoming less so. It is being replaced by the term *bladder pain syndrome*. American Urological Association guidelines have combined the terms.

Originally considered a bladder disease, it is now positioned in the medical spectrum as a chronic pain syndrome that may begin as a pathologic process in the bladder in many, but not all, patients. In a small percentage of patients, it can progress into a disorder that even cystectomy may not benefit!

**IC/BPS encompasses a major portion of the painful bladder disease complex, which includes a large group of patients with bladder and/or urethral and/or pelvic pain, irritative voiding symptoms (urgency, frequency, nocturia, dysuria), and sterile urine cultures.** Painful bladder conditions with well-understood and established etiologies included radiation cystitis, cystitis caused by microorganisms including some that are not detected by routine culture methodologies, and systemic disorders that affect the bladder. **IC/BPS is a diagnosis of exclusion.** It may have multiple causes and represent a final common reaction of the bladder to different types of insults. Essentially, one must be confident that the patient with IC/BPS is not actually suffering from any known treatable cause of bladder pain before making the diagnosis.

## DIFFERENTIAL DIAGNOSIS

***Some potential causes of frequency and urgent desire to void:***

Interstitial cystitis/bladder pain syndrome (IC/BPS)
Urinary tract infection (UTI)
Overactive bladder
Upper motor neuron lesion
Habit
Large fluid intake
Pregnancy
Bladder calculus
Urethral caruncle
Radiation cystitis
Large postvoid residual
Urethral condyloma
Diabetes mellitus
Cervicitis
Periurethral gland infection
Atrophic urethral changes
Chemical irritants: contraceptive foams, douches, diaphragm, obsessive washing
Vulvar carcinoma
Diuretic therapy
Bladder cancer
Urethral diverticulum
Pelvic mass
Chemotherapy
Bacterial urethritis
Renal impairment
Diabetes insipidus
Ketamine cystitis

## Definition

**The American Urological Association guideline defines IC/BPS as "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes."** The term *interstitial cystitis* (IC) has classically been used to describe the clinical syndrome of urgency/frequency and pain in the bladder and/or pelvis that is unrelated to any defined urologic pathology. When considering IC/BPS, the symptom of pain should be broadened to include pressure and discomfort.

Urgency is left out of the definition of IC/BPS because it is the cardinal symptom of overactive bladder (OAB) (a confusable disease) and proves to be unnecessary for definition purposes. One can often separate out those patients with the hypersensitivity of IC/BPS from those with the urgency of OAB by doing a cystometrogram. The OAB patient will generally have uninhibited bladder contractions, whereas the IC/BPS patient will have a stable bladder with hypersensitivity during bladder filling. Simple questions will often suffice to differentiate between the two conditions. “Does your urgency to find a restroom come on suddenly, and is it because you are afraid you will wet yourself, or is it a more gradually appearing sensation of increasing pain and discomfort that you feel in the bladder area?” The former strongly suggests OAB, and the latter is most consistent with IC/BPS. OAB is over 10 times more common in the population than IC/BPS, and the treatment algorithm is very different, making the differential diagnosis critical (Figures 7-1, 7-2, and 7-3).

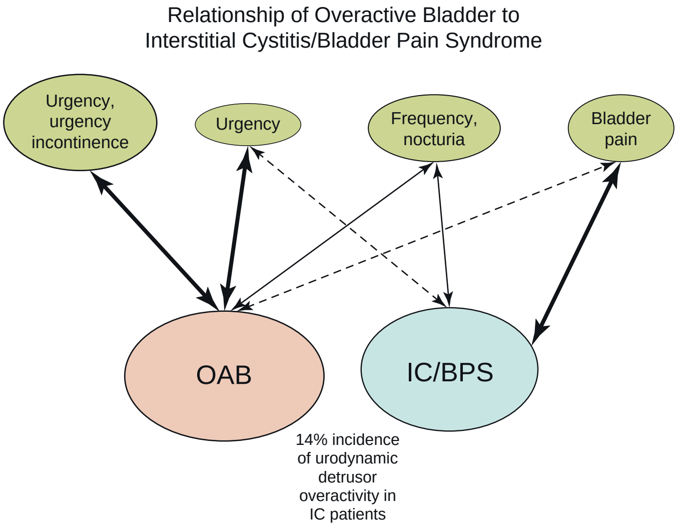
Relationship of Overactive Bladder to
Interstitial Cystitis/Bladder Pain Syndrome
Urgency, urgency incontinence
Urgency
Frequency, nocturia
Bladder pain
OAB
IC/BPS
14% incidence of urodynamic detrusor overactivity in IC patients

**FIGURE 7-1 Relationship of overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome.** (From Abrams P, Hanno P, and Wein A: Overactive bladder and painful bladder syndrome: There need not be confusion. *Neurourol Urodyn* 24:149, 2005.)

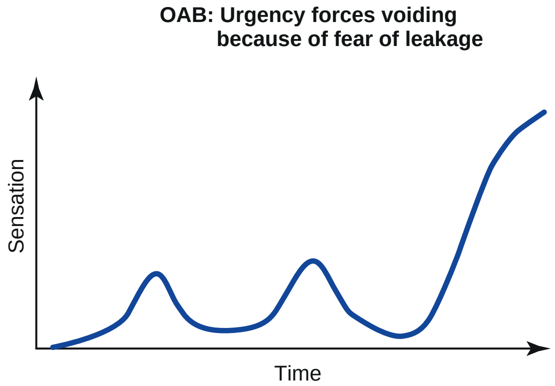

FIGURE 7-2 Undulating onset of true urgency typical of overactive bladder (OAB).

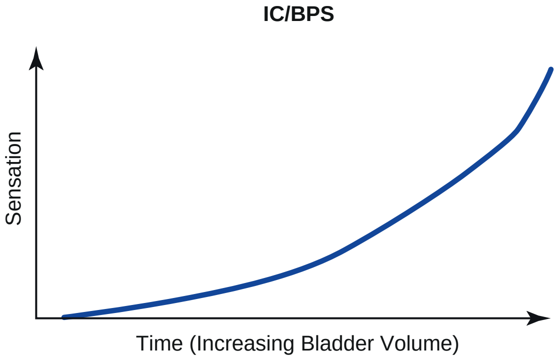

FIGURE 7-3 Steadily increasing pain typical of interstitial cystitis/bladder pain syndrome (IC/BPS).

## Epidemiology

Epidemiology studies of IC/BPS have suffered from the lack of a universally accepted definition, the absence of a validated diagnostic marker or clinical test that assures the diagnosis is made in a uniform manner by different clinicians in different geographic areas, and the lack of a pathognomonic finding on histologic biopsy of bladder tissue. There is considerable variability in studies on incidence and prevalence not only within the United States but around the world. The first population-based study included patients with interstitial cystitis in Helsinki, Finland. The prevalence was 18.1 per 100,000 women and 10.6 per 100,000 population. The annual incidence of new female cases was 1.2 per 100,000. Severe cases accounted for 10% of the total. Only 10% of total cases were in men.

Another early population study from the United States in 1987 first demonstrated the potential extent of what had been considered a very rare disorder. It concluded that while there were 43,500 to 90,000 diagnosed cases of IC/BPS in the United States (twice the prevalence in Finland), up to a half million people had symptoms of painful bladder and sterile urine, considerably expanding the population of potentially affected individuals. The median age at onset was 40 years and there was a 50% remission rate not clearly related to therapy that lasted a mean of 9 months.

More recent epidemiologic studies using different operational definitions have yielded wildly disparate data, from 35 to 24,000 per 100,000 in the United States, to 1.2 per 100,000 in Japan and 7 per 100,000 in the Netherlands. Most studies show a female-to male preponderance of 5:1 or greater. Population-based studies using the O'Leary-Sant Interstitial Cystitis Symptom Index generally show a prevalence of 300 per 100,000 persons. **The Rand Corp., in the largest population-based study in the United States to date, suggested that 2.7% of the adult female population has symptoms suggestive of IC/BPS**. In the absence of a validated marker, it may be difficult to differentiate chronic pelvic pain syndrome (CPPS) in men (nonbacterial prostatitis) from BPS. **In males who have chronic pain they associate with the bladder in the presence of urinary frequency but in the absence of urinary infection, IC/BPS should be considered high in the differential diagnosis.** Men with primarily pain complaints in the absence of any voiding dysfunction fit the more classic description of type 3 CPPS. Only 10% to 20% of patients with IC/BPS in most series have true isolated inflammatory bladder lesions on endoscopy that tend to crack and bleed with distention (Hunner lesions). Men tend to be diagnosed at an older age than women and have a higher incidence of Hunner lesion.

All patients with presumed IC/BPS with microhematuria should undergo cystoscopy, urine cytology, and bladder biopsy of any suspicious lesion to be sure that a bladder carcinoma is not present. Bladder carcinoma in situ can result in symptoms similar to IC/BPS. It would seem that in the absence of microhematuria and with a negative cytology, the risk of missing a cancer is negligible but not zero. **There is no evidence that IC/BPS itself is associated with a higher risk of bladder cancer or transitions to cancer over time.** It is important that the clinician be aware of symptoms of the following disorders, which may be associated with some cases of IC/BPS: Depression, Sjögren syndrome, irritable bowel syndrome, allergies, fibromyalgia, chronic fatigue syndrome, dyspareunia, and focal vulvitis.

## Etiology

**It is likely that IC/BPS has a multifactorial etiology** (Figure 7-4). A "leaky epithelium," mast cell activation, neurogenic inflammation, primary pelvic floor dysfunction, and sequelae of bladder infection or pelvic surgery have all been proposed at one time or another. There is little data to support the role of an active infectious etiology, but it is conceivable that a viral or bacterial cystitis could begin the cascade that ultimately leads to a self-perpetuating process resulting in chronic bladder pain and voiding dysfunction.

## Diagnosis

**The diagnosis of IC/BPS is the recognition of chronic pain, pressure, and/or discomfort associated with the bladder, usually accompanied by urinary frequency in the absence of any identifiable cause.** A high index of suspicion is required on the part of the clinician because many patients suffer for years in the absence of the correct diagnosis. **Pelvic pain and urinary frequency lasting more than 6 weeks and unrelated to urinary infection establishes a working diagnosis.** Some patients will not complain of pain, but if the clinician asks them why they void so often, they will admit to a "pressure" or "discomfort" that is relieved, at least momentarily, by emptying the bladder.

An intravesical potassium chloride challenge (KCl test) has been proposed for diagnosis. It compares the sensory nerve provocative ability of sodium versus potassium using a 4 M potassium chloride solution. Pain and provocation of symptoms by potassium constitutes a positive test. The test has low sensitivity and low specificity, failing to diagnose at least 25% of IC/BPS patients presenting with classic symptoms and overdiagnosing much of the population who actually have OAB, urinary infection, and

The discovery of antiproliferative factor (APF) by Susan Keay and her group at the University of Maryland represents a potential major advance in the search for the etiology of IC/BPS and perhaps even in the quest for a more rational treatment approach. It remains to be confirmed by other laboratories around the world. Dr. Keay observed that cells from the bladder lining of normal control subjects grow significantly more rapidly in culture than cells from IC/BPS patients. Normal bladder cells were cultured in the presence of urine from patients with IC/BPS, asymptomatic controls, bacterial cystitis, and vulvovaginitis. Only urine from IC/BPS patients inhibited bladder cell proliferation. The presence of APF was found to be a sensitive and specific biomarker for IC/BPS. It was found in bladder urine but not in renal pelvic urine of IC/BPS patients, indicating production by the bladder urothelial cells. Subsequent studies indicated that APF is associated with decreased production of heparin-binding EGF-like growth factor (HB-EGF). APF activity was related to increased production of epidermal growth factor (EGF), insulin-like growth factor 1, and insulin-like growth factor binding protein 3 by the bladder cells from IC patients but not by the cells from healthy bladders. Studies of IC/BPS patients and asymptomatic controls showed urine levels of APF, HB-EGF, and EGF to reliably differentiate IC/BPS from controls.

APF may or may not prove to be an accurate marker of IC/BPS. It appears to have the highest sensitivity and specificity of the variety of possible markers tested, and it fits nicely into the etiologic schema portrayed in Figure 7-4. It has been shown to differentiate men with bladder-associated pain and irritative voiding symptoms from those with pelvic/perineal pain alone and other nonspecific findings compatible with the chronic pelvic pain syndrome in men (CPPS III), previously categorized as nonbacterial prostatitis.

It has been hypothesized by Keay and colleagues that IC/BPS may result from an inhibition of bladder epithelial cell proliferation caused by the APF, which is mediated by its regulation of growth factor production from bladder cells. Conceivably, any of a variety of injuries to the bladder from a traumatic or infectious process *in a susceptible individual* may result in IC/BPS if APF is present and suppresses production of HB-EGF. Theoretically, if production of APF could be “turned off” by genetic techniques, or if its effects were nullified by exogenous HB-EGF, the clinical syndrome might be prevented.

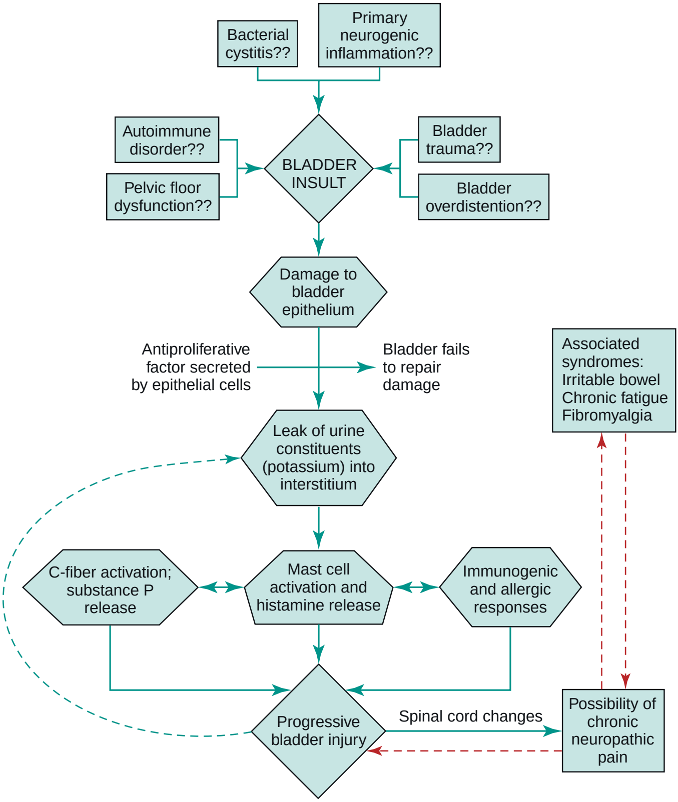
Bacterial cystitis??
Primary neurogenic inflammation??
Autoimmune disorder??
Pelvic floor dysfunction??
BLADDER INSULT
Bladder trauma??
Bladder overdistention??
Damage to bladder epithelium
Antiproliferative factor secreted by epithelial cells
Bladder fails to repair damage
Associated syndromes: Irritable bowel Chronic fatigue Fibromyalgia
Leak of urine constituents (potassium) into interstitium
C-fiber activation; substance P release
Mast cell activation and histamine release
Immunogenic and allergic responses
Progressive bladder injury
Spinal cord changes
Possibility of chronic neuropathic pain

**FIGURE 7-4** Etiology of interstitial cystitis/bladder pain syndrome (IC/BPS). (From Hanno PM: Bladder pain syndrome (interstitial cystitis) and related disorders. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh Urology*, ed 10, Philadelphia, 2011, Saunders, pp. 357-401.)

nonspecific pelvic pain as having IC/BPS. Prospective and retrospective studies looking at the KCl test for diagnosis in patients presenting with symptoms of IC/BPS have found no benefit of the potassium test in comparison with standard techniques of diagnosis. The American Urological Association Guideline does not recommend its use.

Several IC/BPS symptom scales have been developed. They are designed to evaluate the *severity* of symptomatology and monitor disease progression or regression with or without treatment. They have not been validated as diagnostic instruments.

Because IC/BPS is a diagnosis of exclusion, one must rule out infection, overactive bladder, and less common conditions including but not limited to carcinoma, eosinophilic cystitis, malakoplakia, schistosomiasis, scleroderma, and detrusor endometriosis. In men under the age of 50, videourodynamics are useful to eliminate other treatable causes of voiding dysfunction. Many drugs including cyclophosphamide, aspirin, NSAIDs, and allopurinol have caused a nonbacterial cystitis that resolves with drug withdrawal. Illicit use of ketamine can cause a fulminant sterile cystitis, which is recognized as a major problem in many parts of Asia.

**In the presence of microhematuria, local cystoscopy is essential to rule out bladder cancer or other lesions.** Cystoscopy under anesthesia with bladder distention can identify the typical mucosal “cracking and bleeding” upon distention that one sees with Hunner lesion (Figure 7-5), present in about 10% to 20% of patients with IC/BPS. However, this procedure is not mandatory to diagnose the syndrome, and it is certainly justifiable to begin conservative therapy without endoscopy or bladder distention having been performed. **Bladder biopsy is indicated only if necessary to rule out other disorders that might be suggested by the cystoscopic appearance.** Glomerulations (petechial bleeding points) (Figure 7-6) are not specific for IC/BPS, and only when seen in conjunction with

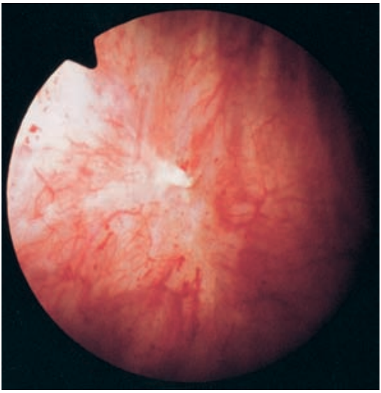

FIGURE 7-5 Typical appearance of Hunner lesion on initial endoscopy and prior to distention, mucosal tearing, and bleeding.

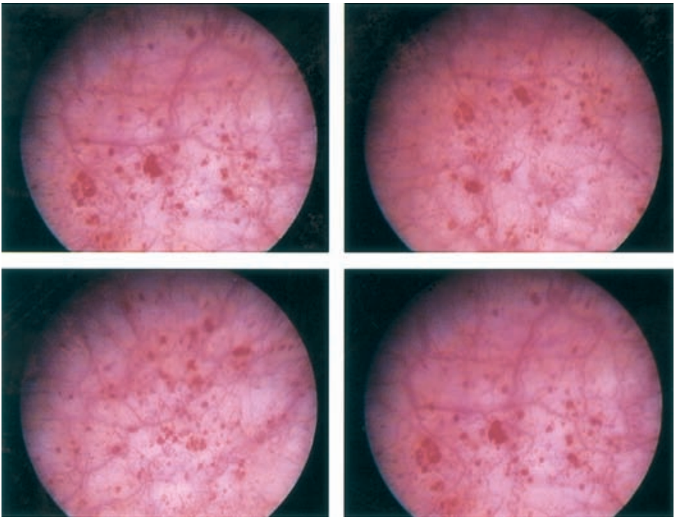

FIGURE 7-6 Typical appearance of glomerulations after bladder distention under anesthesia.

the clinical criteria of bladder pain and frequency can the finding of glomerulations be viewed as possibly relevant. They can be seen in asymptomatic patients as an incidental finding during routine cystoscopy, after radiation therapy in patients with bladder carcinoma, and after exposure to toxic chemicals or chemotherapeutic agents. They are often identified in patients on dialysis, patients with gravity incontinence, or after urinary diversion — all conditions in which the bladder has not filled for prolonged periods. They are absent in many patients with IC/BPS.

## Initial Management

After diagnosis, the first decision the practitioner faces is whether to institute therapy. If the patient has not had an empiric course of antibiotics for their symptoms, such a trial with one course of treatment is not unreasonable. Doxycycline is a good choice. Generally, patients diagnosed with IC/BPS have already been on several courses of antibiotics by the time the diagnosis is even entertained.

If the patient's symptoms are mild to moderate, the withholding of immediate medical treatment is worth considering. Someone who awakens once or twice a night and voids at 2- to 3-hour intervals with minimal pain symptoms would be unlikely to benefit further from active treatment. **Data that early intervention affects the natural history or course of the disease is lacking, and an argument for the early institution of therapy cannot be supported on the basis of epidemiologic data or clinical trials**. Patient education and empowerment is an important initial step in therapy. Reassuring the patient that this is not a life-threatening disease, that others have similar problems and have learned to live with them, that there is a spontaneous remission rate, and that symptoms do not invariably progress does much to alleviate the stress that accompanies the diagnosis. The Interstitial Cystitis Association is an important resource for information and support for patients (www.ichelp.org).

Timed voiding and behavioral modification can be useful in the short term, especially in patients where frequency rather than pain predominates. Many clinicians believe that stress reduction, exercise, warm tub baths, and efforts by the patients to maintain a normal lifestyle all contribute to quality of life. While elaborate dietary restrictions and an "IC diet" are unsupported by any peer-reviewed literature, many patients do find their symptoms are adversely affected by specific foods and would do well to avoid them. Often these include caffeine, alcohol, and beverages that might acidify the urine such as cranberry juice.

As pelvic floor dysfunction is a commonly associated problem and in some cases may be the primary trigger of perceived bladder pain, pelvic floor physical therapy with myofascial trigger point release and intravaginal Thiele massage administered by an experienced physical therapist can be an excellent therapeutic approach with little in the way of side effects. Education and conservative therapy help many patients, but often more active intervention is required.

## Oral Therapy

While many oral medications have been tried for the treatment of IC/BPS, amitriptyline, pentosan polysulfate sodium, and hydroxyzine remain the only commonly used medications outside of research trials.

**Amitriptyline has become one of the most popular oral agents for the treatment of IC/BPS.** It is an old, inexpensive tricyclic antidepressant available only in its generic form. This class of medication has at least three main pharmacologic actions: 1) central and peripheral anticholinergic activity, 2) blockage of the active transport system in the presynaptic nerve ending responsible for the reuptake of serotonin and norepinephrine, and 3) sedation that may be central or related to antihistaminic properties. It is believed that amitriptyline has analgesic properties and potentiates the body's own endorphins. It may help to stabilize the mast cells in the bladder and also increase bladder capacity through its effect on the beta-adrenergic receptors in the bladder body. Finally, the sedative effects can help the patient sleep.

The physician prescribing amitriptyline should be very familiar with the drug because it has many significant side effects. These commonly include daytime sedation, constipation, increased appetite, and dry mouth. It should not be prescribed for potentially suicidal patients or for those with cardiac problems or arrhythmias. The patient with IC/BPS should be started on a dose of 10 mg before bed. The dose is gradually increased by 10 mg each week to a maximum dose of 50 mg at bedtime at the start of the fifth week. If tolerated, this dose is maintained.

IC expert C. Lowell Parsons' suggestion that a defect in the epithelial permeability barrier, the glycosaminoglycan layer, contributes to the pathogenesis of IC/BPS has led to an attempt to correct such a defect with the synthetic sulfated polysaccharide sodium pentosan polysulfate (PPS). This is a heparin analogue (trade name *Elmiron*), which is sold in an oral formulation. Three to 6 percent of each dose is excreted into the urine. Two placebo-controlled multicenter trials in the United States served as the pivotal studies for Food and Drug Administration (FDA) approval for the pain of interstitial cystitis. In the initial study, overall improvement of greater than 25% was reported by 28% of the PPS-treated group versus 13% in the placebo group. In the follow-up study, the respective figures were 32% on PPS versus 16% on placebo. Average voided volume on PPS increased by 20 cc. No other objective improvements were documented. A National Institute of Diabetes and Digestive and Kidney Diseases study, looking at both PPS and hydroxyzine alone and in combination compared to placebo, failed to show a statistically significant response to either medication. Two FDA mandated phase 4 studies have been completed. The first showed no dose response from 300 mg total daily dosage PPS to 900 mg total daily dosage. The second failed to demonstrate any efficacy comparing the 300 mg daily dose to placebo. **At best, Elmiron appears to have a modest beneficial effect in a minority of patients who take it for 3 to 6 months.** There is no convincing data that a longer trial is worthwhile in nonresponders. The dose is 100 mg three times daily. Side effects include a 4% incidence of reversible hair loss, gastrointestinal (GI) upset, and skin rash. It is generally well tolerated though not highly efficacious.

Antihistamines have been used for their properties blocking the effects of mast cell activation. Hydroxyzine, an H1 antagonist, was studied in 40 patients treated with 25 mg before bedtime, increasing to 50 mg at night and 25 mg in the morning in those for whom sedation from the medicine was not a problem. The vast majority of patients had symptom improvement, but these good results have not been confirmed in placebo-controlled trials. Cimetidine, an H2 antagonist, has been reported effective in a British trial, but confirmatory studies are lacking and the mechanism of action is unexplained. It is not commonly used.

Improvement with systemic steroids was first described in 1953. They have fallen out of favor due to the risk of chronic administration. It has been reported that prednisone at a dose of 25 mg daily for 1 to 2 months and then tapered as tolerated may be effective in patients with otherwise unresponsive ulcerative disease.

While the exact role of autoimmunity in the etiology of IC/BPS remains controversial, Finnish studies have demonstrated good results with low-dose cyclosporine, an antirejection medication used in organ transplantation. In a direct comparison with PPS, cyclosporine-treated patients had a 75% response rate compared to a 19% response rate with Elmiron. Significant side effects include hypertension, creatinine elevation, headache, paresthesia, gingival hyperplasia, GI pain, gingival pain, increased hair growth, paresthesias, flushing, muscle pain, shaking, emesis, and risks of lymphoma.

## Intravesical Therapy

**Dimethyl sulfoxide (DMSO) is the only FDA-approved medication for intravesical instillation for the treatment of IC/BPS.** It is a product of the wood pulp industry and a derivative of lignin.

It has exceptional solvent properties and is freely miscible with water, lipids, and organic agents. Pharmacologic properties include membrane penetration, enhanced drug absorption, anti-inflammatory, analgesic, collagen dissolution, muscle relaxant, and mast cell histamine release. Intravesical delivery by urethral catheter of 50 ml of a 50% solution (*Rimso-50*) allowed to remain in the bladder for 15 minutes and repeated at weekly intervals for 6 weeks is effective in ameliorating symptoms in about 60% of patients for a period of several months to over a year. Some patients who respond to an initial 6-week course are treated monthly for 6 months. Patients emit a garliclike odor for several hours after treatment and may experience a short-term symptom exacerbation. It is often administered as part of a "cocktail" including 10 mg triamcinolone (*Kenalog*), 44 meq sodium bicarbonate, and 40,000 units heparin.

Heparin, an exogenous glycosaminoglycan, can be administered intravesically in sterile water as a single agent. Forty thousand units in 20 cc of sterile water self-administered via catheter daily and held for 30 to 60 minutes has been reported beneficial, but no placebo-controlled studies have confirmed efficacy. Intravesical lidocaine solutions may have some short-term therapeutic benefit in some patients.

The possible therapeutic value of intra-detrusor injection of botulinum toxin type A is currently being determined in clinical trials. It appears to be a potentially promising addition to the armamentarium, but patients need to be willing to intermittently catheterize for days to weeks if post injection urinary retention occurs.

## Hydrodistention

**Hydrodistention under anesthesia is often the first therapeutic modality employed as part of the diagnostic evaluation**. There is no one "correct" way to do this procedure. Our method is to perform a cystoscopic examination (which is often unremarkable), obtain urine for cytology, and distend the bladder for 1 to 2 minutes at a pressure of 60 cm $H_2O$. The bladder is emptied and then refilled to look for glomerulations or ulceration (see Figures 7-5 and 7-6). A therapeutic hydraulic distention follows for another 8 minutes. Biopsy, if indicated, is performed after the second distention with the bladder contracted. Little is to be gained by distending the bladder to more than 1 L volume, even if the pressure of 60 cm has not been reached, and the risk of temporary retention seems to increase as the volume infused increases. While over 50% of patients may experience some symptom relief after distention, this is often transitory and rarely lasts longer than 6 months. In those where relief is prolonged, it is worth considering a repeat distention in the future for therapy. A finding of a bladder capacity of less than 200 cc under anesthesia does not bode well for the success of nonsurgical therapeutic efforts.

## Neuromodulation

Sacral nerve stimulation (SNS) involves implanting permanent electrode(s) to stimulate S3 or S4 roots. In 1989, urologists at the University of California San Francisco showed that stimulation of S3 may modulate detrusor and urethral sphincter function. FDA approved the usage of sacral neuromodulation for treating refractory detrusor overactivity in 1997 and for urinary urgency and frequency in 1999. Although the effectiveness of SNS for detrusor overactivity is largely confirmed by a good number of papers, only a relatively few papers report the effect of SNS in treating IC/BPS. It has not been approved by regulatory authorities specifically for this diagnosis.

## Surgical Therapy

The surgical therapy of IC/BPS is an option after all trials of conservative treatment have failed. IC/BPS, although a cause of significant morbidity, is a nonmalignant process. **Surgery should be reserved for the motivated and well-informed patient who falls into the category of having extremely severe, unresponsive disease, a group which comprises fewer than 10% of patients**. Surgical intervention is aimed at increasing the functional capacity of the bladder or diverting the urine stream. Augmentation (substitution) cystoplasty and urinary diversion with or without cystectomy have been used as a last resort with good results in selected patients.

## Philosophy of Management

A reasonable management algorithm developed by an international committee for the International Consultation on Incontinence 2012 meeting is presented in Figure 7-7. While there

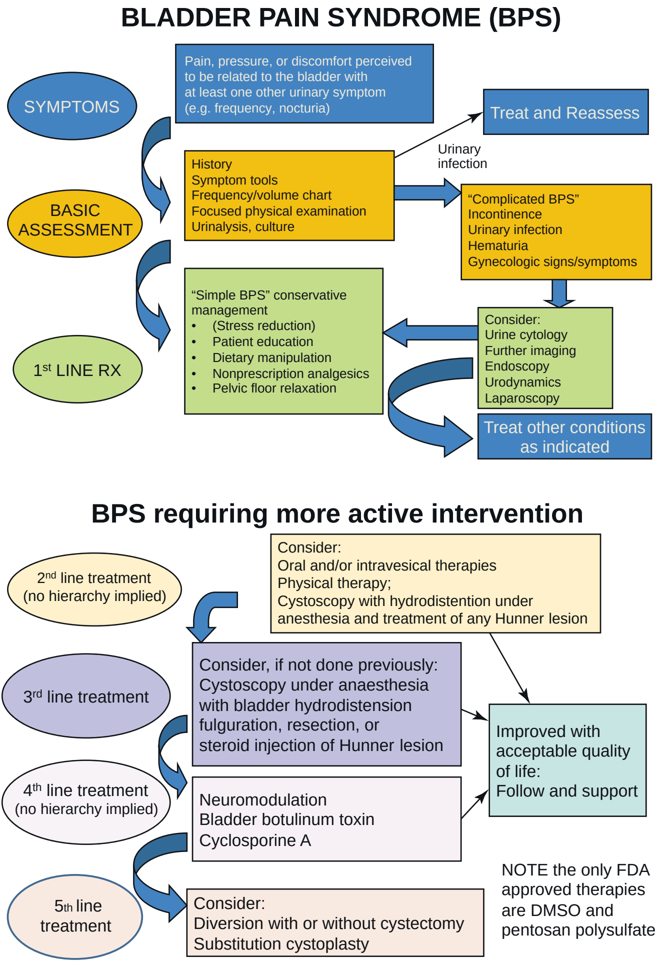
BLADDER PAIN SYNDROME (BPS)
SYMPTOMS
Pain, pressure, or discomfort perceived to be related to the bladder with at least one other urinary symptom (e.g. frequency, nocturia)
BASIC ASSESSMENT
History
Symptom tools
Frequency/volume chart
Focused physical examination
Urinalysis, culture
Urinary infection
Treat and Reassess
"Complicated BPS"
Incontinence
Urinary infection
Hematuria
Gynecologic signs/symptoms
1st LINE RX
"Simple BPS" conservative management
(Stress reduction)
Patient education
Dietary manipulation
Nonprescription analgesics
Pelvic floor relaxation
Consider:
Urine cytology
Further imaging
Endoscopy
Urodynamics
Laparoscopy
Treat other conditions as indicated
BPS requiring more active intervention
2nd line treatment (no hierarchy implied)
Consider:
Oral and/or intravesical therapies
Physical therapy;
Cystoscopy with hydrodistention under anesthesia and treatment of any Hunner lesion
3rd line treatment
Consider, if not done previously:
Cystoscopy under anaesthesia with bladder hydrodistension fulguration, resection, or steroid injection of Hunner lesion
Improved with acceptable quality of life:
Follow and support
4th line treatment (no hierarchy implied)
Neuromodulation
Bladder botulinum toxin
Cyclosporine A
NOTE the only FDA approved therapies are DMSO and pentosan polysulfate
5th line treatment
Consider:
Diversion with or without cystectomy
Substitution cystoplasty

**FIGURE 7-7 Suggested management algorithm.** (5th International Consultation on Incontinence, Recommendations of the International Scientific Committee: Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence. *European Urology*, 2013.)

are many differences of approach to treatment, this author believes that it is best to progress through a variety of treatments. Whereas the shotgun approach of initial multimodal therapy has many adherents, employing or adding one treatment at a time makes the undulating natural history of the disease itself an ally in the treatment process. One should encourage patients to maximize their activity and live as normal a life as possible, not becoming a prisoner of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself. Therefore patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare. Dogmatic restriction and diet are to be avoided unless they are shown to improve symptoms in a particular patient.

## CLINICAL PEARLS

1. Differentiating interstitial cystitis/bladder pain syndrome (IC/BPS) from overactive bladder can be as simple as asking the patient what sensation they experience that makes them feel a tremendous desire to void. Fear of leaking suggests overactive bladder (OAB); increasing pain, pressure, or discomfort suggests bladder pain syndrome (BPS).
2. If symptoms warrant a trial of amitriptyline, be sure to start at a very low dose (10 mg before bed) and increase the dose every 1 to 2 weeks by 10 mg, up to a maximum dose of 50 mg at the fifth week. Side effects, especially sedation, are often the limiting factor in use of the drug.
3. Start with conservative management and add therapies as necessary, stopping therapies that have proven ineffective. Some patients will do well with monotherapy, and others will need multiple interventions at the same time. Throwing the kitchen sink at the patient early in the therapeutic process leaves you with nowhere to go therapeutically except for very invasive treatments that may not prove effective. Time itself can be therapeutic.
4. When hydrodistending the bladder to look for Hunner lesions or in trying to get a therapeutic response, do not distend the bladder beyond a liter of capacity even if the pressure remains less than 60 cm. Distention over a liter carries a risk of retention and may have no added benefit.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## Self-Assessment Questions

1. *What symptoms are characteristic of interstitial cystitis/bladder pain syndrome (IC/BPS)?*
2. *What disorders need to be considered in the differential diagnosis of IC/BPS (confusable disorders)?*
3. *How can the physician differentiate overactive bladder (OAB) from IC/BPS?*
4. *What other pain disorders have been associated with IC/BPS?*
5. *What is the place of surgery in the treatment of IC/BPS?*

## SUGGESTED READINGS

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2. Fitzgerald MP, Payne CK, Lukacz ES, et al: Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness, *J Urol* 187:2113–2118, 2012.
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# CHAPTER 8

# Nephrolithiasis

Justin Ziemba, MD • Phillip Mucksavage, MD

## Epidemiology

1. The annual rate of new onset nephrolithiasis in the United States is 85 cases per 100,000 persons.
2. **The prevalence of nephrolithiasis has increased from 5.2% in 1994 to 8.8% in 2010.**
3. The overall prevalence of nephrolithiasis in the United States is 8.8%.
4. Approximately 1 in 11 individuals has reported a history of nephrolithiasis in the United States.
5. The prevalence is 10.6% in males and 7.1% in females; the incidence is 105 cases per 100,000 males and 68 cases per 100,000 females.
6. Females have two-thirds the risk of developing nephrolithiasis as compared to males.
7. Non-Hispanic white individuals have the highest prevalence of nephrolithiasis, followed by non-Hispanic black and then Hispanic individuals.
8. In screening populations, approximately 8% of individuals will have incidental asymptomatic kidney stones detected with CT.
9. **Of these asymptomatic stones, 15% to 20% will spontaneously pass, 15% to 30% will become symptomatic, 30% to 45% will increase in size, and 5% to 25% will require intervention.**

## Composition of Renal Stones

1. Calcium oxalate (dihydrate and monohydrate): 70%.
2. Calcium phosphate (hydroxyapatite): 20%.

3. Mixed calcium oxalate and calcium phosphate: 11% to 31%.
4. Uric acid: 8%.
5. Magnesium ammonium phosphate (struvite): 6%.
6. Cystine: 2%.
7. Miscellaneous: xanthine, silicates, and drug metabolites, such as indinavir (radiolucent on x-ray and CT scan).

## Pathogenesis and Physiochemical Properties

### GENETICS

1. Idiopathic hypercalciuria
   a. Polygenic
   b. Calcium salt stones
   c. Rare nephrocalcinosis
   d. Rare risk of end-stage renal disease

2. Primary hyperoxaluria types 1, 2, and 3
   a. Autosomal recessive
   b. Pure monohydrate calcium oxalate stones (whewellite)
   c. Nephrocalcinosis
   d. Risk of end-stage renal disease

3. Distal renal tubular acidosis (RTA)
   a. Autosomal recessive or dominant
   b. Apatite stones
   c. Nephrocalcinosis
   d. Risk of end-stage renal disease

4. Cystinuria
   a. Autosomal recessive associated with a defect on chromosome 2
   b. Cystine stones
   c. No nephrocalcinosis
   d. Risk of end-stage renal disease

5. Lesch-Nyhan syndrome (HGPRT deficiency)
   a. X-linked recessive
   b. Uric acid stones
   c. No nephrocalcinosis
   d. Risk of end-stage renal disease

## ENVIRONMENTAL

1. Dietary factors
    a. **Normal dietary calcium intake is associated with a reduced risk of calcium stones secondary to binding of intestinal oxalate.**
    b. Increased calcium and vitamin D supplementation may increase the risk of calcium stones.
    c. Increased dietary sodium intake is associated with an increased risk of calcium and sodium urinary excretion, which leads to increased calcium stones.
    d. Increased dietary animal protein intake may lead to increased uric acid and calcium stones.
    e. Increased water intake is associated with a reduced risk of all types of kidney stones.
2. Obesity
    a. Obesity and weight gain are associated with an increased risk of developing kidney stones.
3. Diabetes
    a. Diabetes is a risk factor for the development of kidney stones.
    b. Insulin resistance may lead to altered acidification of the urine and increased urinary calcium excretion.
4. Geographical factors
    a. The highest risk of developing kidney stones is in the southeastern United States; the lowest risk is in the northwestern United States.
    b. Stone incidence peaks approximately 1 to 2 months after highest annual temperature.

## PATHOPHYSIOLOGY OF STONE FORMATION

1. Idiopathic calcium oxalate
    a. Approximately 70% to 80% of incident stones are calcium oxalate.
    b. Initial event is precipitation of calcium phosphate on the renal papilla as Randall plaques, which serve as a nucleus for calcium oxalate precipitation and stone formation.
    c. Calcium oxalate stones preferentially develop in acidic urine (pH less than 6.0).
    d. Development depends on supersaturation of both calcium and oxalate within the urine.

## PHYSICAL AND BIOCHEMICAL PROPERTIES OF STONE FORMATION

1. Supersaturation
   a. Necessary for a phase change from a solution to a solid
   b. Supersaturation depends on the pH, temperature, and ionic species of the solution.
   c. Thermodynamic solubility product is the concentration at which saturation is reached and crystallization ***is possible***.
   d. The formation product is the concentration at which spontaneous crystallization ***is inevitable.***
   e. The metastable zone refers to the area between the thermodynamic solubility product and the formation product where no spontaneous crystallization occurs, but existing crystals can grow and new crystallization can occur on a seed.
2. Crystal formation
   a. Nucleation is the first step in crystal formation and can be either homogenous or heterogeneous.
      1) Homogenous nucleation occurs only in pure solutions (i.e., not urine).
      2) Heterogeneous nucleation, which requires a lower supersaturation value than homogenous nucleation, occurs in urine, and crystallization can begin on cellular components and other crystals.
   b. Epitaxy refers to the ability of one crystalline structure to facilitate the nucleation of another crystalline structure.
   c. Once nucleation has occurred, crystals grow via aggregation or agglomeration.
   d. Crystal retention occurs in the renal tubules and is thought to be required for stone formation via two mechanisms, either the free particle or fixed particle hypothesis.
      1) The free particle hypothesis states that nucleation occurs within the renal tubular lumen and that rapid crystal growth traps the stone within the lumen.
      2) The fixed particle hypothesis requires the adherence of the crystals to nearby structures, such as the renal epithelium, which facilitates crystal growth and stone formation.

3. Inhibitors and promoters
   a. Differences in urinary inhibitors and promoters may explain the variability of stone formation in patients with supersaturated urinary components.
   b. Inhibitors can prevent crystal aggregation.
      1) **Common inhibitors include citrate, magnesium, Tamm-Horsfall protein, and glycosaminoglycans.**
   c. Promoters can enhance crystal aggregation.
      1) Common promoters include cellular matrix, oxalate, low urine volume, and epitaxy.
4. Pathogenesis of stone formation
   a. Crystal-induced renal injury
      1) Experimental models have demonstrated that hyperoxaluria leads to oxalate deposition within the renal epithelium.
      2) Deposition of oxalate leads to oxidative stress and formation of reactive oxygen species, which injure the renal epithelium.
      3) Stone formation then preferentially develops through crystal adherence to the injured renal epithelium.
   b. Randall plaques
      1) **Calcium phosphate deposits are noted within the basement membrane of the inner medullary collecting duct of the thin loop of Henle presumably caused by abnormal calcium handling.**
      2) The calcium phosphate deposits enlarge throughout the interstitium and ultimately erode through the epithelium at the tips of the renal papilla.
      3) This deposit of calcium phosphate serves as a nucleus for secondary calcium oxalate stone formation.
   c. Low urinary inhibitors
      1) May be thought of as a balance between the supersaturation of the solutes promoting crystallization and urinary inhibitors opposing crystallization.
      2) Urinary citrate is an inhibitor of calcium stone formation by binding to calcium to reduce supersaturation and prevent nucleation.
   d. Stasis
      1) May be a factor in anatomically abnormal kidneys, such as in ureteropelvic junction obstruction or hydronephrosis.
      2) Hypothesis that stasis prevents urinary washout of crystals.

2. Idiopathic hypercalciuria
   a. Identified in 30% to 60% of calcium oxalate stone formers and in 5% to 10% of nonstone formers
   b. The upper limit of normal for urinary calcium excretion is 250 mg/day for women and 300 mg/day for men.
   c. Need to exclude hypercalcemia, vitamin D excess, hyperthyroidism, sarcoidosis, and neoplasm.
   d. Diagnosed via exclusion in patients with a normal serum calcium but elevated urinary calcium on a random diet.
3. Absorptive hypercalciuria
   a. Increased jejunal absorption of calcium possibly caused by elevated calcitriol (1,25 dihydroxy vitamin $D_3$) levels and increased vitamin D receptor expression.
   b. Divided into type I, II and III, depending on whether urinary calcium levels can be affected by calcium in the diet (type I and II) or renal phosphate leak leading to increased calcium absorption (type III).
   c. Increased calcium absorption leads to a higher filtered load of calcium delivered to the renal tubule.
   d. The treatment for each subtype is generally the same, so determining which type (often requiring inpatient evaluation) is no longer necessary.
   e. Normal serum calcium
4. Renal hypercalciuria
   a. Impaired proximal tubular reabsorption of calcium leads to renal calcium wasting.
   b. Normal serum calcium; hypercalciuria persists despite a calcium restricted diet.
   c. Distinguished from primary hyperparathyroidism by normal serum calcium levels and secondary hyperparathyroidism.
5. Resorptive hypercalciuria
   a. Primary hyperparathyroidism is the underlying mechanism.
   b. Increased PTH levels cause bone resorption and intestinal calcium absorption, which leads to elevated serum calcium that exceeds the reabsorptive capacity of the renal tubule.
   c. Normal to slightly elevated serum calcium
6. Hypercalcemic hypercalciuria
   a. Primary hyperparathyroidism, hyperthyroidism, sarcoidosis, vitamin D excess, milk alkali syndrome, immobilization, and malignancy

7. Hyperoxaluria
   a. The upper limit of normal for urinary oxalate excretion is 45 mg/d in women and 55 mg/d in men.
   b. Acts as a potent inhibitor of stone formation by complexing with calcium
   c. Dietary hyperoxaluria is related to increased consumption of oxalate-rich foods, and/or a low-calcium diet, which by reducing the availability of intestinal calcium to complex to oxalate, allows an increased rate of free oxalate absorption by the gut.
   d. Enteric hyperoxaluria can be caused by small bowel disease or loss, exocrine pancreatic insufficiency, or diarrhea, all of which reduce small bowel fat absorption, leading to an increase in fat complexing with calcium, and thereby facilitating free oxalate absorption by the colon.
   e. Primary hyperoxaluria is a genetic disorder in one of two genes, which results in increased production or urinary excretion of oxalate. In type I, which is an autosomal recessive trait, AGXT (alanine-glyoxylate aminotransferase) is deficient in the liver. This results in increased production of oxalate. These patients develop early oxalosis, stone formation, and ultimate renal failure. In type II, there is a deficiency in D-glycerate dehydrogenase and glyoxylate reductase, which leads to increased urinary oxalate excretion; this type is extremely rare with only 21 reported cases.

8. Hypocitraturia
   a. The lower limit of normal is less than 500 mg/d for women and 350 mg/d for men.
   b. Acts as an inhibitor of stone formation by complexing with calcium.
   c. Citrate is regulated by tubular reabsorption, and reabsorption varies with urinary pH. In acidic conditions, tubular reabsorption is enhanced, which lowers urinary citrate levels.
   d. Diseases that cause acidosis, such as chronic diarrhea or distal RTA, cause lower urinary citrate levels. Thiazide therapy can also reduce citrate levels via potassium depletion.
   e. In the majority of patients with hypocitraturia, no etiology is identified, and these patients are classified as having idiopathic hypocitraturia.

9. Hyperuricosuria/uric acid stones
   a. Approximately 5% to 10% of incident stones are uric acid.
   b. The upper limit of normal is greater than 750 mg/d for women and 800 mg/d for men.
   c. Uric acid is a promoter for calcium oxalate stone formation by serving as a nucleus for crystal generation and also by reducing the solubility of calcium oxalate.
   d. A low urinary pH is critical for uric acid stone formation. At a urinary pH less than 5.5, uric acid exists in its insoluble undissociated form, which facilitates uric acid stone formation. As the urinary pH increases, the dissociated monosodium urate crystals are predominant and serve as a nucleus for calcium-containing stone formation.
   e. Increased uric acid production is common in patients with a high dietary intake of animal protein, in myeloproliferative disorders, and in gout. However, uric acid stone formation is also common in patients with diabetes and the metabolic syndrome presumably caused by insulin resistance, which impairs renal ammonia excretion necessary for urinary alkalization.

10. Cystinuria
    a. In both men and women, urinary cystine excretion exceeds 350 mg/d.
    b. Caused by autosomal recessive disorder involving the SLC3A1 amino acid transporter gene on chromosome 2
    c. The dibasic amino acid transporter, which is located within the tubular epithelium, facilitates reabsorption of dibasic amino acids, such as cystine, ornithine, lysine, and arginine, (COLA). A defect in this enzyme leads to decreased cystine reabsorption and increased urinary excretion of cystine.
    d. Cystine solubility rises with increasing pH and urinary volume.
    e. Positive urine cyanide-nitroprusside colorimetric reaction is a qualitative screen.

11. Calcium phosphate stones
    a. Approximately 12% to 30% of incident stones are calcium phosphate.

   b. Calcium phosphate stones preferentially develop in alkaline urine (pH greater than 7.5).
   c. Calcium phosphate stones can be present as either apatite or brushite (calcium phosphate monohydrate).
   d. Overalkalinization with potassium citrate for hypercalciuria can sometimes lead to calcium phosphate stones.

12. Struvite stones/triple phosphate/infection stones
    a. Approximately 5% of incident stones are struvite.
    b. Struvite stones are composed of magnesium ammonium phosphate and calcium phosphate. They may also contain a nidus of another stone composition.
    c. Often grow to encompass large areas in the collection system or staghorn calculi.
    d. Urinary tract infections (UTIs) with urease splitting organisms, which include *Proteus spp*., *Klebsiella spp*., *Staphylococcus aureus*, *Pseudomonas spp*., and *Ureaplasma spp*., are required to split urea into ammonia, bicarbonate, and carbonate.
    e. A urinary pH greater than 7.2 is required for struvite stone formation.
    f. Conditions that predispose to urinary tract infections increase the likelihood of struvite stone formation. Struvite stones are common in patients with spinal cord injuries and neurogenic bladders.

## Clinical Manifestations of Nephrolithiasis

1. Presentation
   a. Asymptomatic kidney stones are found in 8% to 10% of screening populations undergoing a CT scan for unrelated reasons.
   b. Pain is the most common presenting symptom in the majority of patients.
      1) The stone produces ureteral spasms and obstructs the flow of urine, which causes a resultant distention of the ureter, pyelocalyceal system, and ultimately the renal capsule to produce pain.
      2) Renal colic is characterized by a sudden onset of severe flank pain, which often lasts 20 to 60 minutes. The pain is paroxysmal, and patients are often restless and unable to get comfortable.

3) **Three main sites of anatomic narrowing or obstruction are within the ureter: the ureteropelvic junction, the lumbar ureter at the crossing of the iliac vessels, and the ureterovesical junction.**
4) The location of pain generally correlates with these sites of anatomic narrowing: the ureteropelvic junction produces classic flank pain, the midureter at the level of the iliac vessels produces generalized lower abdominal discomfort, and the ureterovesical junction produces groin or referred testes/labia majora pain.

c. Associated nausea and vomiting are frequent. Fever and chills are common with concomitant UTI.

d. Dysuria or strangury, which is the desire to void but with urgency, frequency, straining, and small voided volumes, is possible with stones located at the ureterovesical junction.

**DIFFERENTIAL DIAGNOSIS**

Pyelonephritis: Fever with associated flank pain
Musculoskeletal pain: Pain with movement
Appendicitis: Right lower quadrant tenderness at McBurney point
Cholecystitis: Right upper quadrant tenderness with Murphy sign
Colitis/diverticulitis: Left lower quadrant tenderness with GI symptoms
Testicular torsion: Abnormal testicular exam with high-riding testicle
Ovarian torsion/ruptured ovarian cyst: Adnexal tenderness

## Evaluation of Patients with Nephrolithiasis (Figure 8-1)

1. General considerations
   a. All patients in the acute phase of renal colic should have a history and physical, a urinalysis, a urine culture if urinalysis demonstrates bacteruria or nitrites, and a serum creatinine. If the patient presents with fever, then a complete blood count should also be included.
   b. All patients with a first stone episode should undergo a basic evaluation with a medical history including family history, dietary history, and medications; physical exam and ultrasound; blood analysis with creatinine, calcium, and uric acid; urinalysis and culture; and stone analysis.

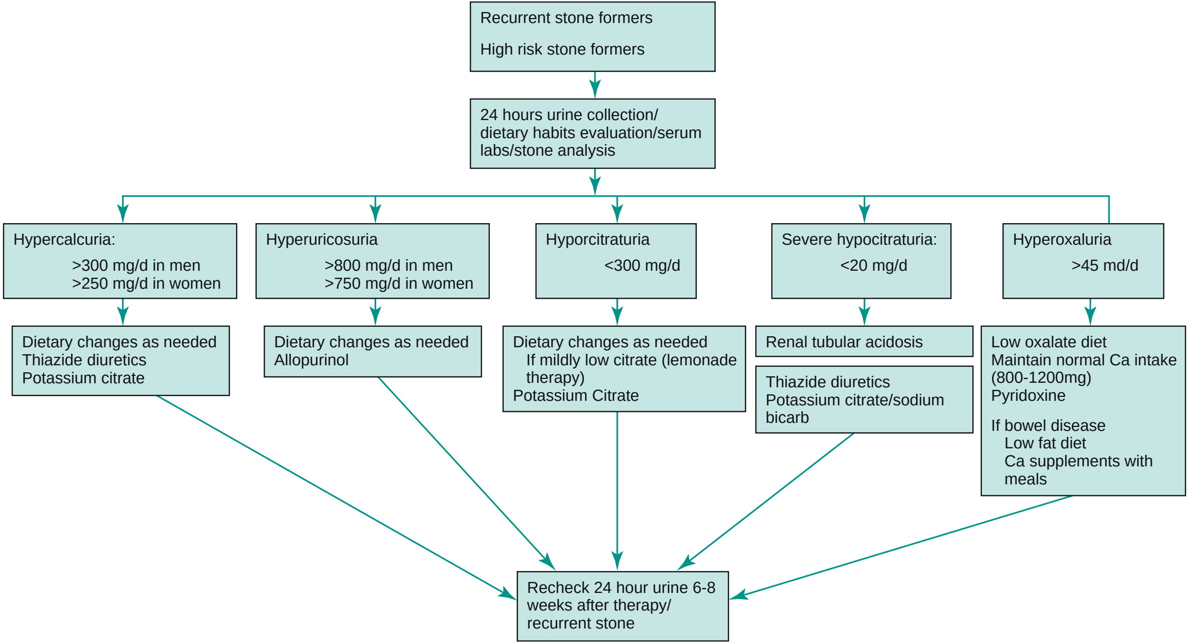

FIGURE 8-1 Treatment algorithm for a patient with recurrent stone disease.

   c. Patients at high risk include those with a family history of nephrolithiasis, recurrent stone formation, large stone burden, residual stone fragments after therapy, solitary kidney, metabolic, or genetic abnormalities known to predispose to stone formation, stones other than calcium oxalate, and children given a higher rate of an underlying metabolic, anatomic, and/or functional voiding abnormality. These patients they should undergo the basic evaluation, plus two 24-hour urine collections, at least 4 weeks following the acute stone episode. Further therapy will be guided by the stone analysis and 24-hour urine collections.

2. Medical history
   a. General medical history is mandatory in all stone formers.
   b. Past medical history with a specific focus on diseases known to contribute to stone formation, including inflammatory bowel disease, previous bowel resection, or gastric bypass, hyperparathyroidism, hyperthyroidism, RTA, and gout.
   c. Family history is of particular importance because a positive family history is a risk factor for incident stone formation and recurrence.
   d. Review medications for drugs known to increase stone formation, such as acetazolamide, ascorbic acid, corticosteroids, calcium-containing antacids, triamterene, acyclovir, and indinavir.
   e. Dietary history can also be relevant, especially in those with high- or low-calcium diets, diets high in animal protein, and diets with significant sodium intake.

3. Physical exam
   a. May provide clues to underlying systemic diseases.

4. Laboratory evaluation
   a. Urinalysis
      1) Specific gravity may indicate relative hydration status.
      2) Calcium oxalate stones preferentially form in a relatively acidic pH (less than 6.0), whereas calcium phosphate stones preferentially form in a relatively alkaline pH (greater than 7.5). A low pH (less than 5.5) is mandatory for uric acid stone formation. A high pH (greater than 7.2) is critical for struvite stone formation. A pH constantly greater than 5.8 may suggest an RTA.

    3) Microscopy may reveal red blood cells, white blood cells (WBCs), and bacteria.
    4) **Crystalluria can define stone type: Hexagonal crystals are cystine, coffin lid crystals are calcium phosphate, and rhomboidal crystals are uric acid.**

b. Urine culture is mandatory if microscopy reveals bacteriuria, if struvite stones are suspected, or if symptoms or signs of infection are present.

c. Electrolytes
    1) Calcium (ionized or calcium with albumin): Elevated calcium may suggest hyperparathyroidism, and a parathyroid hormone (PTH) blood test should be done.
    2) Uric Acid: Elevated uric acid is common in gout and, in conjunction with a radiolucent stone, is suggestive of uric acid nephrolithiasis.

d. A complete blood count (CBC) may show mild peripheral leukocytosis. WBC counts higher than 15,000/mm$^3$ may suggest an active infection.

e. Ammonium chloride load test: Identifies distal or Type I RTA. Oral ammonium chloride load (0.1 gm/kg body weight) given over 30 minutes will not raise the urinary pH greater than 5.4 if a Type I RTA is present.

f. Sodium nitroprusside test: Identifies cystinuria. Addition of sodium nitroprusside to urine with cystine concentration higher than 75 mg/L alters the urine color to purple-red.

g. **24-Hour urine collection**: Typically one to two 24-hour urine collections are obtained at least 6 weeks after an acute stone event or following initiation of medical therapy or dietary modification. Collection is done to determine total urine volume, pH, creatinine, calcium, oxalate, uric acid, citrate, magnesium, sodium, potassium, phosphorus, sulfate, urea, and ammonia. Cystine is also determined if a cystine screening test is positive. Supersaturation indices are also calculated. An adequate collection is determined by total creatinine, which is 15-19 mg/kg for women and 20-24 mg/kg for men. (Table 8-1)

h. Stone analysis: Performed either with infrared spectroscopy or x-ray diffraction. It provides information about the underlying metabolic, genetic, or dietary abnormality.

TABLE 8-1 **Normal Values of Urinary Excretion of Substances Affecting Stone Formation**

| Substance | Men (mg/day) | Women (mg/day) |
|---|---|---|
| Urinary calcium | < 300 | < 250 |
| Urinary uric acid | 800 | < 750 |
| Urinary citrate | 50-600 | 650-800 |
| Urinary oxalate | 45 | < 45 |

5. Imaging considerations
   a. A noncontrast CT scan is the recommended initial imaging modality for an acute stone episode. A noncontrast CT scan has a sensitivity of 98% and a specificity of 97% in detecting ureteral calculi. A low-dose noncontrast CT scan (less than 4 mSv) is preferred in patients with a body mass index (BMI) less than 30. When a ureteral stone is visualized on a noncontrast CT scan, it will be demonstrated 50% of the time on a CT scan scout film.
   b. A renal bladder ultrasound is the recommended initial imaging modality in both children and pregnant patients in order to limit ionizing radiation. Ultrasonography has a median sensitivity of 61% and a specificity of 97%. If ultrasonography is equivocal, and the clinical suspicion is high for nephrolithiasis, then a low-dose noncontrast CT scan may be performed in both children and pregnant patients.
   c. Plain film of the kidneys, ureters, and bladder (KUB) is also routinely used. Conventional radiography with a KUB has a median sensitivity of 57% and a specificity of 76%. Pure uric acid, cystine, indinavir, and xanthine stones are radiolucent, and are not visible on KUB.
   d. Historically, intravenous pyelography (IVP) was commonly utilized for diagnosis of stone disease because it could readily identify radiolucent stones and define calyceal anatomy. It has a median sensitivity of 70% and a specificity of 95%. However, CT has largely replaced IVP.
   e. Magnetic resonance imaging is generally not performed for urolithiasis because of cost, low sensitivity, and time needed to acquire images.
   f. **A combination of ultrasonography and KUB is recommended for monitoring patients with known radiopaque**

**ureteral calculi on medical expulsion therapy** because this limits costs and radiation exposure. Those with radiolucent stones will require a low-dose noncontrast CT scan.

g. Following surgical intervention with ureteroscopy or shock-wave lithotripsy, imaging may be performed. If it is to be performed, the recommended imaging modality is ultrasonography because it is inexpensive and has no ionizing radiation. A KUB may also be performed because of low levels of radiation.

h. **Limiting radiation exposure is a critical component of modern diagnostic imaging, especially in patients with stone disease.** Imaging modalities with ionizing radiation should conform to the ALARA principle or as low as reasonably achievable. A renal ultrasound has 0 mSv, a KUB has 0.7 mSv, an IVP has 3.0 mSv, a low-dose noncontrast CT scan has 3.0 mSv, and a standard CT scan has 10.0 mSv.

## Management of Nephrolithiasis

### MEDICAL THERAPY (TABLE 8-2)

1. All stone formers
   a. High fluid intake of 2.5-3.0 L/day with urine volume greater than 2 L/day
   b. **Normal calcium diet of 800-1200 mg/day, preferably not through supplements.** Avoid excess calcium supplementation; however calcium citrate is preferred if indicated.
   c. Limit sodium to 4-5 g/day.
   d. Limit animal protein to 0.8-1.0 g/kg/day.
   e. Limit oxalate-rich foods.
   f. Maintain a normal BMI and physical activity.
   g. Targeted therapy depending on underlying metabolic abnormality and/or 24-hour urine collection results

2. Calcium oxalate stones
   a. Dietary hyperoxaluria: Limit oxalate-rich foods.
   b. Enteric hyperoxaluria: Limit oxalate-rich foods and calcium supplementation with greater than 500 mg/day.
   c. Primary hyperoxaluria: Pyridoxine can decrease endogenous production of oxalate. The dose is 100-800 mg/day.

TABLE 8-2 **Medications for the Medical Management of Urolithiasis**

| Indication | Drug | Usual Dose | Stone Type |
|---|---|---|---|
| Hypercalciuria (renal leak/ absorptive) | Thiazide | 25-50 mg BID | Calcium oxalate, calcium phosphate |
| | Hydrochlorthiazide | 50 mg QD | |
| | Chlorthalidone | 1.25-2.5 mg QD | |
| | Indapamide | | |
| Hypocitraturia, urinary alkalinization, hypokalemia (especially with thiazides) | Potassium citrate | 10-20 mEq TID | Calcium oxalate, uric acid, cystine |
| Hyperuricosuria | Allopurinol | 100-300 mg daily | Uric acid, calcium stones |
| Cystinuria | d-Penicillamine | 250-500 mg QID | Cystine |
| | Alpha-mercaptopropionyl-glycine (tiopronin) | 200-400 mg TID | |
| | Captopril | 150 mg QD | |
| Absorptive hypercalciuria (second-line agents after thiazides) | Sodium cellulose phosphate | 5 gm BID/TID | Calcium oxalate |
| | Potassium phosphate | 250 mg TID/QID | |
| Urease inhibitor | Acetohydroxamic acid | 250 mg TID/QID | Struvite/infection stones |

   d. Hypocitraturia: Potassium citrate both raises the urinary pH out of the stone-forming range and restores the normal urinary citrate concentration. Sodium bicarbonate may also be used, if unable to tolerate potassium supplementation.
   e. Hypercalciuria: **Thiazide diuretics, which inhibit a sodium-chloride co-transporter, therefore enhancing distal tubular sodium reabsorption via the sodium-calcium co-transporter to promote tubular calcium reabsorption. Thiazides decrease urinary calcium by as much as 150 mg/day.**

3. Calcium phosphate stones
   a. Primary hyperparathyroidism: Requires parathyroidectomy.
   b. Distal RTA (Type I): Potassium citrate or sodium bicarbonate to restore the natural pH balance.

4. Struvite/infection stones
   a. Total stone removal because each fragment harbors urease-producing bacteria and serves as a nidus for further stone growth.
   b. Appropriate antibiotic therapy to eradicate the urease-producing bacteria
   c. Restoration of normal pH with urinary acidification with L-methionine or inhibition of urease enzyme with acetohydroxamic acid

5. Uric acid stones
   a. Low animal protein diet
   b. Specific therapy depends on 24-hour urine collection results.
   c. Alkalinization of the urine with potassium citrate or sodium bicarbonate for stone dissolution is possible with a pH of 7.0 to 7.2 and for maintenance of a stone-free state with a pH of 6.2 to 6.8.
   d. Hyperuricosuria (with or without hyperuricemia): Allopurinol at 100-300 mg/day, which inhibits xanthine oxidase to reduce uric acid production.

6. Cystine stones
   a. Increase daily fluid intake to 3.5 to 4.0 L/day.
   b. Specific therapy depends on 24-hour urine collection results.
   c. Alkalinization of the urine with potassium citrate or sodium bicarbonate above a pH of 7.5 to improve solubility of cystine threefold

   d. D-penicillamine is a chelating agent that forms a disulbond with cysteine to produce a more soluble compound, thereby preventing the formation of cysteine into the insoluble, stone forming, cystine. Alpha-mercaptopropionyl-glycine (tiopronin) is the preferred alternative to D-penicillamine, as it has a better safety and efficacy profile. Alpha-mercaptopropionyl-glycine reduces the disulfide bond of cystine to form the more soluble cysteine, again reducing stone formation. Lastly, captopril is an angiotensin-converting enzyme inhibitor, which can reduce cystine, but its role in therapy is not yet well defined.

## ACUTE RENAL COLIC

1. General considerations
   a. Primary considerations include symptomatic control with analgesics, antiemetics, and adequate hydration.
   b. First-line analgesia is generally a nonsteroidal antiinflammatory, such as ketorolac.
   c. Patients should be instructed to sieve their urine for collection of stone fragments.
   d. **Spontaneous stone passage occurs in 80% of patients with sizes less than 4 mm. With sizes greater than 10 mm, there is a low probability of spontaneous passage.** Location also influences spontaneous stone passage rates, with proximal ureteral stones passing 25% of the time, midureteral stones passing 45% of the time, and distal ureteral stones passing 70% of the time. When stones are going to pass spontaneously, the majority pass within 6 weeks.
   e. Referral to a urologist is necessary with persistent pain, high-grade obstruction, bilateral obstruction, presence of infection, solitary kidney, abnormal anatomy, failure of conservative management, large stone burden, pregnancy, or in children.
2. Medical expulsive therapy
   a. Alpha-blockers, such as tamsulosin, and calcium channel blockers (nifedipine) or steroids can facilitate stone passage via ureteral smooth muscle relaxation.
   b. Alpha-blockers are the preferred medication in expulsive therapy because they increase the rate of spontaneous passage of ureteral calculi by nearly 30% and are routinely used by urologists for benign prostatic hyperplasia (BPH).

   c. Use of alpha-blockade also decreases time to pass the stone, rates of ureteroscopy and hospitalization, and time off from work.
   d. Medical expulsive therapy (MET) is acceptable in patients with ureteral calculi less than 10 mm who have well-controlled pain, no evidence of infection, adequate renal function, and no other contraindications to the therapy.
   e. MET with any agent is an off-label use for the medications and should only be used for 28 to 45 days. The medication should be discontinued after stone passage.
   f. Patients should undergo a course of MET for 4 to 6 weeks and be reassessed with imaging or undergo treatment if unable to pass the stone.

## SURGICAL THERAPY

1. Shock wave lithotripsy (SWL):
   a. Shock waves are high-energy focused-pressure waves that can travel in air or water. When passing through two different mediums of different acoustic impedance, energy is released, which results in the fragmentation of stones. Shock waves travel harmlessly through substances of the same acoustic density. Because water and body tissues have the same density, shock waves can travel safely through skin and internal tissues. The stone is a different acoustic density and, when the shock waves hit it, they shatter and pulverize it. Urinary stones are thus fragmented, facilitating in their spontaneous passage.
   b. Treatment success depends on stone size, location, composition, hardness, and body habitus. For renal stones, upper or middle polar stones are ideally treated with SWL, whereas lower pole stones have a clearance rate as low as 35%. Stone burden is also important; stone clearance rates decrease with stones greater than 20 mm in size. Stone composition or hardness influences stone fragmentation with calcium oxalate monohydrate, calcium phosphate (brushite), and cystine stones being relatively resistant to shock waves. Furthermore, dense stones, as measured on preoperative CT, with greater than 1000 Hounsfield units (HU), require a greater number of shocks for fragmentation. Finally, body habitus, as measured by skin-to-stone distance on preoperative CT, also

influences success. A decrease in stone-free rates have been observed with skin-to-stone distances of greater than 10 cm.

   c. Ideally all stones less than 1 cm in any location in the kidney can be treated with SWL. Stones greater than 1 cm in the lower pole should undergo ureteroscopy or percutaneous nephrolithotomy. **Stones between 1-2 cm in the middle or upper pole with favorable characteristics on noncontrast CT (SSD less than 10 cm, HU greater than 1000) can be successfully treated with SWL.**
   d. According to guidelines for the American Urological Association (AUA) and the European Association of Urology (EAU), SWL can be offered as first-line therapy for ureteral stones less than 10 mm. The stone-free rates are 82% in the proximal ureter, 73% in the midureter, and 74% in the distal ureter. Placement of a ureteral stent to facilitate stone fragment passage is not necessary prior to SWL. For stones less than 10 mm in the mid and distal ureter, SWL can be offered, but higher success rates are achieved with ureteroscopy. For ureteral stones less than 10 mm, SWL is not recommended.
   e. Contraindications of SWL include (absolute) pregnancy, bleeding diathesis, and obstruction below the level of the stone; and (relative) calcified arteries and/or aneurysms and cardiac pacemaker.
   f. Other methods to improve SWL success include decreasing the rate of shocks (60 shocks per minute), minimizing air pockets between the patient and coupling head, alpha-blockers (tamsulosin) administered after treatment, percussive therapy and inversion (for lower pole stones).
   g. Complications of SWL include skin bruising, subscapular and perinephric hemorrhage, pancreatitis, urosepsis, and Steinstrasse ("street of stone," which may accumulate in the ureter and cause obstruction).

2. Percutaneous nephrolithotomy (PCNL)
   a. The technique is establishment of access at a lower pole calyx, dilation of the tract with a balloon dilator or Amplatz dilators under fluoroscopy, and stone removal with graspers or its fragmentation using electrohydraulic, ultrasonic, or laser lithotripsy. A nephrostomy tube or ureteral stent is left for drainage.

b. Staghorn calculi are large branched stones that conform to the shape of the calyceal anatomy and fill the collecting system. Partial staghorn calculi are smaller and only fill a portion of the collecting system. Typically, staghorn and partial staghorn calculi are composed of struvite, but uric acid and cystine stones also can form staghorn calculi. Staghorn calculi can lead to recurrent infections, sepsis, renal failure, and possibly death.

c. **According to the AUA, treatment for staghorn and partial staghorn calculi is best managed with PCNL.** Overall, the stone-free rate with PCNL is 78%. Stone-free rates are three times greater with PCNL than with SWL, and on average PCNL requires a fewer number of overall procedures (1.3 versus 2.8). Furthermore, for lower pole stones greater than 1 cm, PCNL has a stone free rate of greater than 90%, compared to less than 25% for SWL.

d. Additional candidates for PCNL include cystine calculi, which are large volume and resistant to SWL, and anatomic abnormalities, such as those with ureteropelvic junction (UPJ) obstruction, caliceal diverticula, obstructed infundibula (hydrocalyx), ureteral obstruction, malformed kidneys (e.g., horseshoe and pelvic), and obstructive or large adjacent renal cysts.

e. Contraindications of PCNL include uncontrolled bleeding diathesis, untreated urinary tract infection (UTI), and inability to obtain optimal access for PCNL because of obesity, splenomegaly, or interposition of colon.

f. Complications of PCNL include hemorrhage (5% to 12%), perforation, and extravasation (5.4% to 26%), damage to adjacent organs (1%), ureteral obstruction (1.7% to 4.9%), and infection/urosepsis (3%).

3. Retrograde intrarenal surgery (ureteroscopy [URS])

   a. Instrumentation includes both rigid and flexible ureteroscopes. Rigid ureteroscopes are ideally suited for access to the distal ureter but can be utilized up to the proximal ureter. Flexible ureteroscopes are ideally suited for ureteral and intrarenal access. Stones are removed using the stone basket or graspers. Alternatively, endoscopic lithotripsy devices are used for stone fragmentation (electrohydraulic, ultrasonic, or laser lithotripsy).

   b. According to AUA and EAU guidelines, for ureteral stones less than 10 mm, URS can be offered as first-line therapy because URS has higher stone-free rates than SWL (97% versus 86%). Overall, URS has success rates of 93% to 97% in the distal ureter, 78% to 91% in the midureter, and 79% to 80% in the proximal ureter. Although the clinical guidelines recommend either SWL or PCNL for larger intrarenal calculi, URS has become the de facto gold standard for intrarenal stones less than 1.5 cm with stone-free rates of 50% to 80%. Stenting after uncomplicated URS may not be necessary.
   c. URS may be safely performed in patients with morbid obesity, pregnancy, and bleeding diathesis.
   d. Complications include failure to retrieve the stone, mucosal abrasions, false passages, ureteral perforation, complete ureteral avulsion, and ureteral stricture.

4. Open/laparoscopic/robotic surgery
   a. Since the introduction of minimally invasive techniques such as SWL, URS, and PCNL, open surgery has been reduced to rates of 1% to 5%.
   b. Indications for open stone surgery include complex stone burden, treatment failure with endoscopic techniques, anatomic abnormalities, and a nonfunctioning kidney.
   c. Laparoscopic or robotic surgery can be used in place of open techniques, but because of the complexity and rarity of these procedures, they are generally referred to centers of excellence.

## CLINICAL PEARLS

***Nephrolithiasis***

1. Stones less than 1 cm, less than 10 cm skin-to-stone distance, and less than 1000 HU have the highest chance of success after being treated with SWL.
2. Medical expulsive therapy results in faster stone passage, less pain, less hospitalization, and less need for surgical interventions.
3. Low-dose CT scan is the imaging modality of choice when diagnosing a ureteral stone.
4. Stone location in the ureter can often be deduced by the distribution of pain or symptoms.
5. Normal dietary intake of calcium (800-1200 mg) is necessary to prevent stones; too little or too much puts patients at risk of developing future stones.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *A 36-year-old woman presents to your office with a 0.8-cm stone in the upper pole of her left kidney. The patient has a BMI of 29 and recurrent UTIs. The CT scan showed a solitary upper pole stone on the left side with a skin-to-stone distance of 8 cm, and average HU of 789. She has never had a stone before but thinks her mother had a cystine or brushite stone. What factors would you take into consideration when counseling the patient about the success of each treatment option?*
2. *What are the options and indications for medical expulsive therapy?*
3. *A 42-year-old obese man (BMI of 36) presents to the emergency room with right flank pain, nausea, and vomiting. A stone is suspected. What is the best imaging study to work up this patient? What imaging studies can be used to follow the patient after treatment?*
4. *What are the indications for shock wave lithotripsy and methods to improve success?*
5. *What dietary factor plays a role in nephrolithiasis?*

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# CHAPTER 9

# Urologic Emergencies

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## Introduction

This **chapter is designed to aid the urologist** when called to the emergency room (ER) or to a hospitalized inpatient **for matters worthy of immediate attention** aside from urinary trauma, stones, sepsis, and sexually transmitted diseases that are topics of specific chapters covered in detail elsewhere in this manual.

## Gross Hematuria

Bleeding from anywhere in the urinary tract may be manifest by passage of visible blood in the urine. In anticipation of this common emergency, the urologist needs available a well-stocked equipment cart including: a variety of catheter types (e.g., coudé, Council, three-way) and sizes; filiforms and followers; sounds; guide wires; a catheter guide or stylet; and flexible cystoscope. **Management involves two phases: 1) ensuring patency of urine flow and hemodynamic stability and 2) determining etiology of hematuria.**

### HEMODYNAMIC STABILITY

1. Check serial Hb/Hct. Transfuse PRN.
2. Correct coagulopathy.

### ENSURE PATENCY OF URINE FLOW

1. If voiding comfortably without clot monitor for spontaneous clearance of hematuria if otherwise stable.
2. If clot present:
    a. Place large bore catheter to evacuate clot.
    b. Saline continuous bladder irrigation to prevent clot reaccumulation

  - c. Hand (Toomey syringe) evacuation of clot in low-capacity or poorly compliant bladders (e.g., postirradiation)

3. Hematuria with indwelling catheter
    - a. Determine appropriate catheter positioning in bladder.
        - 1) Gently irrigate and aspirate for return of irrigant.
        - 2) Check cystogram.
    - b. Replace or upsize catheter for tamponade of urethral bleeding and/or satisfactory drainage.

### DETERMINE ETIOLOGY OF HEMATURIA

1. Urinalysis (UA) and culture and sensitivity (C&S) for urinary tract infection (UTI)
2. Urine cytology
3. CT urography
4. Cystoscopy
5. Angiography

## Urinary Retention

**Relief of infravesical lower urinary tract obstruction in the difficult-to-catheterize patient is the bread and butter of bedside emergency urologic care.**

### NONCATHETERIZED PATIENT

1. History
    - a. Voiding difficulty
        - 1) Benign prostatic hyperplasia (BPH)
        - 2) Urethral stricture
    - b. Prior lower urinary tract trauma or surgery (e.g., transurethral resection of the prostate [TURP], radical prostatectomy)
        - 1) Urethral stricture
        - 2) Bladder neck contracture
        - 3) Meatal stenosis/ balanitis xerotica obliterans (BXO)
    - c. History of bladder stones
    - d. History of sexually transmitted disease (e.g., gonorrhea)
    - e. Gross hematuria – clot urinary retention
    - f. Acute neurologic event – spinal/cerebral shock
        - 1) Spinal cord injury
        - 2) Cerebrovascular accident
        - 3) Multiple sclerosis

2. Physical examination
   a. Palpably distended bladder
   b. Palpable urethral mass
   c. Meatal fibrosis

3. Laboratory tests
   a. Urinanalysis
   b. Blood urea nitrogen (BUN)/creatinine

4. Management
   a. Placement of well-lubricated catheter
      1) Coudé tip for BPH
      2) Catheter guide
   b. If unsuccessful
      1) Van Buren sound to identify urethral level obstruction
      2) Filiforms and followers to dilate stricture
      3) Cystoscopy
         a) Guide wire
         b) Heyman/Amplatz hollow core dilators
      4) Suprapubic tube placement

### CATHETERIZED PATIENT

**Urinary retention in a patient with a Foley catheter previously inserted may be due to malpositioning of catheter (misplacement, false passage, or caudal migration) or obstruction of the catheter lumen by clot, stone, tissue, or debris.**

1. History
   a. Catheter previously draining well
   b. Severe pain during or after placement
   c. Gross hematuria

2. Physical examination
   a. Excess length of catheter protruding from urethral meatus
   b. Palpably distended bladder (if not, consider possible anuria)

3. Management
   a. Irrigate and aspirate to remove debris or clot.
   b. Cystogram to determine catheter position
   c. Replace catheter (follow algorithm for noncatheterized patient).

## Flank Pain

A multitude of entities, both urologic and nonurologic, may be the cause of the patient presenting with acute atraumatic flank pain.

A systematic evaluation will enable the prudent urologist to identify any contributing genitourinary etiologies and formulate further treatment based on this diagnosis.

## DIFFERENTIAL DIAGNOSIS

1. Intrinsic renal/ureteral obstruction
    a. Obstructing calculus
    b. Hematologic/vascular
        1) Blood clot
        2) Papillary necrosis
    c. Infectious
        1) Viscous pyuria/bacteriuria
        2) Fungus ball
        3) Tuberculous pyelitis/ureteritis with secondary stricture of infundibula/ureters
    d. Obstructing tumor
        1) Transitional cell carcinoma
            a) Renal pelvic/calyx
            b) Ureter
            c) Bladder
        2) Adenocarcinoma prostate
    e. Ureteral stricture
2. Extrinsic ureteral obstruction
    a. Cancers and associated adenopathy
        1) Endometrial
        2) Ovarian
        3) Breast
        4) Colon
        5) Sarcoma
    b. Retroperitoneal fibrosis
        1) Idiopathic
        2) Perianeurysmal
    c. Iatrogenic ligation
        1) Clip
        2) Stitch
3. Parenchymal bleed or rupture
    a. Malignant
        1) Renal cell carcinoma
        2) Transitional cell carcinoma
    b. Benign
        1) Cyst rupture or bleed
        2) Angiomyolipoma bleed
    c. Adrenal hemorrhage
4. Renovascular
    a. Occlusive arterial
        1) Intrinsic stenosis/thrombosis (trauma)
        2) Extrinsic emboli
    b. Renal vein thrombosis

## EVALUATION

1. History
   a. Duration of pain
   b. Location
   c. Anticoagulant use
2. Physical examination
   a. Temperature and vital signs
   b. Tenderness
   c. Ecchymosis
   d. Palpable mass
3. Laboratory tests
   a. UA and C&S
   b. Complete blood count (CBC) with differential
   c. Basic metabolic panel (BMP)
   d. Coagulation profile (Coags)
4. Imaging
   a. Ultrasound
      1) Hydronephrosis – nonspecific
      2) Best utilized during pregnancy
   b. Noncontrast CT scan of abdomen and pelvis
      1) Mass
      2) Adenopathy
      3) Stones
         Hounsfield Units (HU) may predict stone composition.
         Indinavir stones are nonvisualized even on CT.
   c. Contrast-enhanced CT scan of abdomen and pelvis
      1) Arterial phase
         Identify renovascular clot or stenosis.
         Enhancing masses
         Parenchymal ischemia
      2) Urographic phase
         Site of obstruction
         Intralumenal filling defects
   d. Retrograde or antegrade urography

## ACUTE MANAGEMENT – BASED ON ETIOLOGY

1. Obstruction
   a. Monitor if stable.
   b. Drainage

    1) Retrograde stent
    2) Antegrade nephrostomy tube or stent
  c. Dilation

2. Infectious
  a. Empiric antimicrobials
  b. Pan culture

3. Hemorrhagic
  a. Anemia: Transfuse PRN.
  b. Reverse anticoagulation.
  c. Endoscopic cauterization

4. Renovascular occlusion
  a. Initiate anticoagulation.
  b. Thrombectomy
  c. Interventional radiologic treatment/angioplasty

## Scrotal Pain

First and foremost, a call to evaluate a patient with acute scrotal pain should lead to a prompt response owing to the possibility that the underlying condition may represent a surgically treatable emergency, namely testicular torsion. Every other cause for acute scrotal pain, aside from genital trauma, is less urgent.

### DIFFERENTIAL DIAGNOSIS

1. Torsion of testis
2. Torsion of appendage
  a. Testis (müllerian remnant)
  b. Epididymis (wolffian remnant)
3. Epididymitis
4. Tumor
5. Referred pain

### EVALUATION

1. Physical examination
  a. Temperature
  b. High-riding testis
    1) c/w torsion due to cord twisting/shortening
  c. Palpable mass
  d. Prehn sign
    1) Elevation of scrotum lessens pain as in epididymitis.

   e. Blue dot sign
      1) Torsed appendage
   f. Scrotal edema/erythema
      1) Nonspecific: Can see in torsion or epididymitis

2. Laboratory tests
   a. UA
   b. White blood cell count (WBC) with differential

3. Imaging
   a. Color Doppler ultrasound of the scrotum
   b. Nuclear scan

### MANAGEMENT

1. Torsion testicle (emergency scrotal exploration mandatory)
   a. **Salvageable**
      1) **Detorsion**
      2) **Ipsilateral testis fixation with nonabsorbable suture**
   b. **Unsalvageable**
      1) **Ipsilateral Orchiectomy**
      2) **Contralateral Testis Fixation with nonabsorbable suture**

2. Epididymitis
   a. Empiric antibiotics if infectious etiology is suspected
   b. NSAIDS
   c. Scrotal rest and elevation

3. Torsion appendage
   a. Excision if noted during incidental exploration
   b. NSAIDS
   c. Scrotal rest and elevation

4. Intratesticular tumor
   a. Check testis tumor markers.
   b. Urgent radical inguinal orchiectomy

## Fractured Penis

Rupture of the corpora cavernosa with a turgid erection, from sheering external blunt trauma usually sustained during sexual activity, merits **urgent evaluation and operative repair, which has been documented to decrease the risk of Peyronie disease and erectile dysfunction compared to nonoperative management.**

## EVALUATION

1. History
   a. Blunt trauma and bending of rigid erection
   b. Acute penile pain and loss of erection
   c. Sensation of popping and/or snap
   d. Possible gross hematuria or voiding difficulty signal urethral involvement.
2. Physical examination
   a. Voided UA re gross hematuria
   b. Buck fascia intact: Edema/ecchymosis limited to phallus
   c. Buck fascia disrupted: Hematoma/urinoma spread along Colles fascia superiorly to anterior abdominal wall, posteriorly to perineum, and inferiorly to thighs
3. **Urethral evaluation mandatory**
   a. Retrograde urethrogram
   b. Possible cystoscopy

## MANAGEMENT

1. Operative penile exploration
2. Repair corpora.
3. Urethroplasty as needed

# Oliguria and Anuria

Urologists are often requested to evaluate an oligo-anuric patient because of the possibility that upper or lower urinary tract obstruction may contribute to renal failure. A systematic evaluation should allow for prompt identification and treatment of anatomic or functional urinary obstruction.

## DEFINITION

1. Anuria - urine output less than 50 mL/24 hr
2. Oliguria - urine output less than 500 mL/24 hr

### DIFFERENTIAL DIAGNOSIS

1. Prerenal azotemia
   a. Volume depletion (dehydration, hemorrhage)
   b. Low cardiac output
   c. Renal artery stenosis
   d. Systemic vasodilation (septic shock, anaphylaxis, drug overdose)

2. Intrinsic renal parenchymal disease
    a. Acute tubular necrosis
    b. Acute glomerulonephritis
    c. Acute interstitial nephritis
    d. Chronic glomerulonephritis
3. Postrenal azotemia
    a. Upper urinary tract obstruction
        1) Calculus
        2) Tumor
        3) Papillary necrosis
        4) Ureteral stricture
    b. Lower urinary tract obstruction
        1) Atonic detrusor/detrusor areflexia
            a) Neurogenic
                i) Spinal cord injury
                ii) Cerebral vascular accident
                iii) Multiple sclerosis
                iv) Peripheral denervation (abdominoperineal resection)
            b) Nonneurogenic
                i) Chronic voiding dysfunction
                ii) Obtunded/drug overdose
        2) Bladder outlet obstruction
            a) Benign prostatic hyperplasia (BPH)
            b) Urethral stricture
            c) Bladder/urethral calculus
            d) Phimosis

## EVALUATION

1. History
    a. Voiding difficulty
    b. Urinary tract stones
    c. Diabetes
    d. Congestive heart failure

2. Physical examination
    a. Signs of dehydration (skin turgor, sunken eyeballs)
    b. Abdominal or flank distension, tenderness, or mass
    c. Palpably distended bladder
    d. Obstructing phimosis, lichen sclerosis of glans, or meatus
    e. Peripheral edema
    f. “Uremic skin frost”

3. Laboratory studies
    a. BUN/Cr electrolyte profile
    b. CBC (especially regarding anemia)
    c. UA (regarding pyuria, hematuria, proteinuria)

4. Urinary tract imaging
    a. Ultrasound or CT scan
        1) Hydroureteronephrosis
            Unilateral
            Bilateral
        2) Renal atrophy or scarring
        3) Echogenic renal parenchyma
    b. Bladder: postvoid residual urinary volume

### MANAGEMENT

1. Circumvent lower urinary tract obstruction.
    a. Foley catheter
    b. Suprapubic tube
2. Circumvent upper urinary tract obstruction.
    a. Ureteral stents
    b. Percutaneous nephrostomy
3. Monitor urine output.
4. Serial BUN/Cr measurement
5. Correct electrolyte profile.
6. Nephrologic evaluation

## Priapism

### DEFINITION

The term priapism is derived from Priapus, the Greek god of fertility and protector of horticulture often depicted with a wooden sickle in his hand and his phallus proudly erect. Priapism refers to a pathological condition of prolonged penile erection unrelated to sexual stimulation or failing to subside following orgasm. Priapism often is associated with penile pain, although the onset of pain may be delayed for 6 to 8 hours. Priapism has been observed in males of all ages, including infants. The age-related peak incidence of priapism follows a bimodal distribution with the highest incidence occurring between the ages of 5 and 10 and between 20 and 50 years old. **The vast majority of causes in the younger age group is secondary to neoplasm or sickle cell disease.**

## CLASSIFICATION

1. Ischemic

**Ischemic, venous, or low-flow priapism refers to a condition of failure of venous outflow with resultant cessation of arterial inflow creating an acidotic and hypoxic environment within the corpora cavernosum.** The net effect creates increased intracorporeal pressure similar to a compartment syndrome and acidosis resulting in painful engorgement and eventual smooth-muscle necrosis, fibrosis, and permanent erectile dysfunction if not expediently reversed.

2. Nonischemic

Nonischemic, arterial, or high-flow priapism is a result of unregulated, increased arterial inflow causing prolonged penile tumescence. Perineal or direct penile trauma is the underlying event causing arterial rupture leading to increased intracorporeal arterial inflow. **The erection in nonischemic priapism is often painless and less than fully rigid.** Nonischemic priapism is significantly less prevalent than ischemic priapism.

## ETIOLOGY AND PATHOPHYSIOLOGY

1. Approximately 50% of all episodes of priapism are thought to be idiopathic.
2. Pharmacotherapy
   a. In adults, inappropriate dosing of intracavernous therapy for erectile dysfunction with vasoactive agents such as alprostadil, papaverine, phentolamine, and combinations thereof is thought to be the most common cause of ischemic priapism. Intraurethral alprostadil suppositories and oral phosphodiesterase inhibitors have a much lower incidence of priapism.
   b. Antidepressants such as trazodone
   c. Antipsychotics such as chlorpromazine, phenothiazine, and clozapine
   d. Antihypertensives such as hydralazine, prazosin, and guanethidine
   e. The high fat content of total parenteral nutrition
   f. Cessation of anticoagulation with heparin or Coumadin may result in a rebound hypercoagulable state.
   g. Recreational drugs such as cocaine or alcohol

3. Hematologic diseases
    a. Sickle cell anemia: The oxygen tension in the corpora cavernosa predisposes to erythrocyte sickling leading to venous stasis and obstruction resulting in priapism.
    b. Leukemia
    c. Hb Olmsted
    d. Thrombophilia
4. Neurological conditions
    a. Lumbar spinal stenosis
    b. Cerebrovascular disease
    c. Seizure disorders
5. Neoplasm: Bladder and prostate cancer have been implicated in metastatic infiltration of the corpora resulting in venous outflow obstruction. This type of priapism is usually treated with chemotherapy or radiation therapy.
6. **Nonischemic priapism usually results from direct trauma to the penis, perineum, or pelvis. The cavernosal artery has been identified as the most commonly injured vessel in nonischemic priapism.**

## EVALUATION

1. History
    a. Duration and quality of erection
    b. Pain or no pain
    c. Medication or recreational drug use
    d. History of sickle disease (less likely sickle cell trait) or hypercoagulable states
2. Physical examination
    a. Penile exam will reveal a rigid, painful erection with a softer glans penis with ischemic priapism, whereas a semierect, painless penis is often noted with nonischemic priapism.
    b. Signs of genital or perineal trauma
    c. Regional lymphadenopathy
3. Laboratory tests
    a. Aspiration of corporeal blood for blood gas measurement
        1) **Ischemic: Dark venous blood**
        **pH less than 7.25, $PO_2$ less than 30, $PCO_2$ greater than 60**

   2) **Nonischemic: Bright red arterial blood pH greater than 7.30, $PO_2$ greater than 50, $PCO_2$ less than 40**

   b. CBC may suggest underlying leukemia. Do a sickle cell prep if appropriate.

4. Doppler ultrasound reveals no cavernosal arterial flow with ischemic priapism, whereas a ruptured cavernosal artery with unregulated blood flow and blood pooling are characteristic of nonischemic priapism.

## TREATMENT OF PRIAPISM

**The ultimate goal of treatment is to cause detumescence that will relieve pain and hopefully decrease the risk for intracorporeal fibrosis that may result in permanent erectile dysfunction in at least 25% of affected patients.** Emergency treatment upon patient presentation is advised because a time-dependent window of opportunity exists for successful resolution of the priapic episode and maintenance of normal erectile function. Treatment generally follows a stepwise approach based on etiology of priapism.

1. Ischemic priapism
   a. The first line of treatment is analgesics or a dorsal penile nerve block for pain control in combination with intracorporeal irrigation and evacuation of old blood from the corpora cavernosa utilizing a 19- to 21-gauge butterfly (scalp) needle. If this is unsuccessful, then injection of an alpha agonist into the corporal space to cause vasoconstriction is advised. Epinephrine, norepinephrine, and phenylephrine have all been utilized. **Phenylephrine, a pure alpha-1 adrenergic agonist with minimal cardiac side effects, has become the agent of choice.** Phenylephrine solution is made by mixing 1 mL of phenylephrine 10 mg/mL with 19 mL of normal saline, resulting in a final phenylephrine solution of 500 mcg/mL. Phenylephrine solution is then instilled in aliquots of 500 mcg every 5 minutes until detumescence occurs or for a series of 10 to 12 injections before deemed unsuccessful. Constant cardiac monitoring of blood pressure and heart rate is advised during treatment with these sympathomimetic agents. Lower concentrations should be used in children and patients with severe cardiovascular disease.

b. Second-line treatments involve the creation of various surgical fistulas between the engorged corpus cavernosum and the glans penis, corpus spongiosum, and dorsal or saphenous veins. It is the hope that these fistulas will spontaneously close sometime after detumescence.

Glans-cavernosal shunts: The Winter shunt is created by inserting a Tru-Cut biopsy needle through the glans penis into the corpora cavernosum under local anesthesia. Removal of several cores of tunica albuginea separating the glans and corpora is advised. The Ebbehoj procedure and Lue T-shunt are performed by inserting a number 10 or 15 scalpel blade vertically through the glans penis into the corpora cavernosa, then rotating the blade 90 degrees and removing it horizontally. The skin of the glans penis may then be approximated with an absorbable suture following manual pressure-assisted evacuation of stagnant intracorporeal blood and detumescence.

Open surgical procedures: An Al-Ghorab shunt is created by dorsal dissection at the level of the coronal sulcus down to the distal tips of the corporal bodies where 5-mm elliptical incisions are made bilaterally and dark, old blood is evacuated until detumescence ensues. The incisions are then closed with absorbable sutures. The Quackels cavernoso-spongiosal shunt is created with the patient in the dorsal lithotomy position through a perineal incision with dissection carried down to the bulb of the corpus spongiosum where incisions are made in the adjacent corpus spongiosum and corpus cavernosum. The corpus cavernosum in then drained of old blood and the two structures sutured together side to side either unilaterally or bilaterally. In the Grayhack procedure, the saphenous vein is transected several centimeters inferior to the inguinal ligament at the saphenofemoral junction, mobilized and tunneled subcutaneously to a second incision at the lateral base of the penis where a tension-free end-to-side anastomosis is made with the corpora cavernosa. Similarly the deep and superficial dorsal veins of the penis have also been used for cavernoso-dorsal venous shunts.

2. Sickle cell-associated priapism

   Initial treatment of sickle cell-associated priapism should include corporal aspiration of old blood and, if unsuccessful, injection of a vasoactive agent. Adjunctive treatments that may have some additional benefit in the sickle cell population include hydration, analgesia, oxygenation, and (exchange) transfusions.

3. Nonischemic priapism

   **The initial management of nonischemic priapism is reassurance and watchful waiting.** These patients can be observed safely for several months for spontaneous closure of the fistula with no increased incidence of erectile dysfunction. Ice packing may cause vasospasm and thrombosis aiding early spontaneous closure. Definitive treatment of **persistent nonischemic priapism requires selective internal pudendal arteriography to identify the fistulous site, followed by selective angiographic embolization**; open surgical ligation is reserved for instances of failed repeat embolization.

## Foreskin Emergencies

### PHIMOSIS

Phimosis is the inability to retract the foreskin over the glans penis due to narrowing, constriction, and/or adhesions. Congenital neonatal foreskin adhesions usually spontaneously lyse during the first several years of life. Forceful retraction of the phimotic foreskin during infancy is ill advised and may result in fissures and eventual scarring of the distal foreskin. Poor genital hygiene may result in chronic infection causing adhesions between the inner foreskin and underlying glans penis, and fibrosis resulting in inability to retract the foreskin. Complications of phimosis include balanitis, posthitis, paraphimosis, voiding dysfunction, and late diagnosis of penile carcinoma.

Patients may present with complaints of erythema, itching, discharge, or pain with sexual intercourse. Minor phimosis can be managed with improved genital hygiene and sometimes topical application of a corticosteroid cream with or without antifungals. Phimosis preventing emergency catheter placement can often be circumvented by use of a coudé catheter, catheter guide, nasal speculum to visualize the meatus, or flexible cystoscope and guide wire placement. Mild balanoposthitis can be treated with broad spectrum oral antibiotics. Severe balanitis may require an emergency dorsal slit aided by local anesthesia. Elective formal circumcision should be considered for persistent symptoms or recurrent infection.

### PARAPHIMOSIS

Paraphimosis refers to the retracted foreskin becoming trapped proximal to the glans penis resulting in edema, inflammation, and pain. Left untreated, it can progress to ischemia of the glans penis and eventual gangrene. Treatment consists of initial firm compression to decrease edema, followed by manual reduction often aided by placement of a lubricant at the level of the proximal glans penis. However, dry gloved hands are essential in gaining traction of the outer foreskin when pulling it back over the glans into the anatomic position. A local anesthetic block can be utilized for pain control during the procedure. In rare instances, direct incision of the constricting band may be necessary to allow manual retraction. Paraphimosis is frequently the result of a partially phimotic +/– foreshortened foreskin; elective circumcision may be indicated.

## Genital Skin Infections

### BALANOPOSTHITIS

Balanitis refers to inflammation of the cutaneous layer of the glans penis, whereas posthitis is inflammation of the prepuce. These two conditions often occur simultaneously and are associated with phimosis. Meticulous genital hygiene is the cornerstone of prevention. Oral antibiotics (e.g., cephalexin) or antifungals (e.g., fluconazole) in combination with cleansing will often lead to resolution.

### SCROTAL ABSCESS

Scrotal and perineal abscesses usually result from infection of a local hair follicle (folliculitis) or sebaceous cyst. It is important to rule out any associated process that may manifest as drainage of pus in the scrotal region such as an epididymal abscess or a tracking perirectal abscess sometimes associated with diverticular disease. Therefore in addition to physical examination, scrotal ultrasound or pelvic CT scan may be indicated. Management of local scrotal abscesses includes treatment with skin-coverage antibiotics (e.g., cephalosporins) combined with incision and drainage of loculated collections if spontaneous drainage does not occur.

## FOURNIER GANGRENE

1. General characteristics
   a. **Fournier gangrene is a fulminant necrotizing fasciitis of the male genitalia and perineum.**
   b. The greatest incidence is between ages 20 and 50 years with no predilection for race.
   c. Mortality rates average 25% despite aggressive treatment.
   d. Initiating events include urethral strictures, perianal abscess, fissures, urethrocutaneous fistulas, genitourinary trauma, and instrumentation.
   e. Predisposing immunocompromised states such as diabetes mellitus, human immunodeficiency virus (HIV), cancer, and chronic ethanol or intravenous drug abuse are often associated.
2. Pathogenesis
   a. Microbiology: **Infections are frequently polymicrobial**. The most frequently cultured organisms include gram-negative rods from the Enterobacteriaceae family and gram-positive streptococci and staphylococci. Anaerobic bacteria, including bacteroides fragilis, streptococci, and clostridia, are often present.
   b. Pathophysiology: **The involved microorganisms act synergistically, causing obliterative endarteritis resulting in soft tissue necrosis and gangrene.** Infection usually involves the skin and subcutaneous tissue, sparing the underlying muscle. Spread of infection may be initially limited by fascial planes such as Buck fascia for infections of urethral origin and Colles fascia for infections of anorectal origin.
3. Diagnosis

   A high index of suspicion is paramount for timely diagnosis and emergency treatment. Patients typically present with a painful and/or erythematous, edematous, foul-smelling genital cellulitis often with areas of eschar or necrosis. Crepitus, caused by gas formation in the infected tissues, is a classic finding associated with anaerobic infection. CT scan will usually reveal subcutaneous gas and any associated abnormalities such as diverticular disease or pelvic fluid collections. These patients are often febrile or frankly septic.

4. Treatment
   a. Do a pan culture and promptly initiate treatment with triple antibiotic coverage (e.g., penicillin G, 3-5 million units/6 hr; gentamicin, 3-5 mg/kg/24 hr; and clindamycin, 600-1200 mg/24 hr). Adjust antibiotics when culture and susceptibility results are known.
   b. Metabolic stabilization with vigorous intravenous hydration; correction of electrolyte imbalances and hyperglycemia
   c. **Perform emergency surgery with wide excision and debridement of all devitalized tissue. Mere incision and drainage has been shown to substantially increase mortality rates.**
   d. Cystoscopy to assess for urethral stricture and suprapubic tube placement
   e. Proctosigmoidoscopy to assess for associated anorectal anomalies and possible bowel diversion
   f. Perform vigilant postoperative wound examination with repeat debridement if necessary for devitalized tissue. Frequently irrigate wound with hydrogen peroxide, bacitracin, etc., and do wet-to-dry dressing changes using 25% Dakin solution.
   g. Adjuvant hyperbaric oxygen therapy decreases the spread of necrotizing fasciitis (especially with gas-forming anaerobic organisms) and promotes wound healing.
   h. Once a clean bed of granulation tissue is noted, closure by a variety of reconstructive techniques, including skin grafting and local flaps, may be undertaken.

## Foreign Bodies

### ZIPPER INJURIES

Zipper-associated genital lacerations should be treated conservatively with initial pressure to minimize bleeding, careful genital hygiene, and topical application of an antibiotic ointment (e.g., Polysporin) to prevent local irritation. Zipper entrapment of the penile or scrotal skin requires emergency zipper disassembly. This is accomplished by using a wire cutter to sever the connective metallic assembly of the zipper allowing the teeth of the zipper to separate. A local anesthetic block may help to control pain during the procedure.

### EXTERNAL RINGS

The use of various types of constricting bands (rings, washers, bolts, pipes), purportedly as “sexual aids,” may result in local tissue edema secondary to compression, making removal challenging. Left in place, tissue necrosis will ultimately ensue. If generous lubrication and compression of local edema does not allow for safe and easy removal, then a standard ring or bolt cutter will need to be utilized. Similarly, a variety of genital piercings, which have recently achieved significant popularity, may serve as a source of inflammation and/or infection necessitating immediate removal.

### INTRAURETHRAL FOREIGN BODIES

Various foreign bodies placed in the urethra may become trapped. Pretreatment identification of the exact type of foreign body and proximal extent of migration is advised. Evaluate with a CT scan or a kidney-ureter-bladder radiograph (KUB) if the object is completely radiopaque (screws, BBs). If feasible, attempt endoscopic extraction. Objects located proximal to the external sphincter, densely embedded, or adherent to local tissue may require open exploration and removal. Irregularly shaped, sharp, or relatively large objects, especially in the posterior urethra, may be least traumatically extracted by endoscopic relocation to the bladder and suprapubic cystotomy. Place a Foley catheter postoperatively to decrease risk for stricture formation in most instances.

## Postcircumcision Complications

1. Infection can usually be treated with an oral cephalosporin.
2. Incision separation, if small, will heal by secondary intent or absorbable suture skin approximation for larger defects.
3. Hematomas, if large and painful, can be evacuated by separation of skin edges and placement of a compressive, but not glans ischemic dressing.
4. Bleeding is usually controlled by application of manual pressure for 10 to 15 minutes. Persistent bleeding may require topical cauterization with a silver nitrate applicator stick or placement of an absorbable suture. Brisk bleeding from the ventral surface is often indicative of laceration of the frenular artery and will require suture ligation for hemostasis.

## Spinal Cord Compression

A multitude of urologic cancers, such as prostate and bladder, may metastasize to the spine. A high index of suspicion and prompt initiation of treatment may be the difference between functional salvage associated with improved quality of life versus permanent paralysis and associated morbidity.

### PRESENTATION

1. Acute extremity weakness or numbness
2. Bone pain

### EVALUATION

1. MRI spine
2. Bone scan

### TREATMENT

1. Empiric medical management
   a. Corticosteroids (e.g., dexamethasone)
   b. Spine stabilization
      1) Cervical collar
      2) Thoracolumbar brace or corset
   c. Deep vein thrombosis (DVT) prophylaxis
2. Radiation oncology evaluation re spot radiation therapy
3. Neurosurgical evaluation re surgical decompression and stabilization

### CLINICAL PEARLS

1. Hyperkalemia is the most common electrolyte abnormality associated with acute renal failure and, if noted, merits further urgent evaluation with an electrocardiogram.
2. Cystoscopy should always be performed during the initial management of Fournier gangrene to identify any predisposing urethral disorder; proctosigmoidoscopy is recommended if the infection is not obviously caused by a disease of the lower urinary tract or surrounding skin.
3. Phenylephrine, a pure alpha-1 adrenergic agonist with minimal cardiac side effects, is the agent of choice for treatment of ischemic priapism with injection therapy.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com**

## *Self-Assessment Questions*

1. *Describe the various imaging modalities available to diagnose acute obstruction in cases of stone, intrinsic or extrinsic tumor, blood clot, or pregnancy.*
2. *What are the underlying medical conditions which predispose to acute renovascular occlusion (arterial, venous)?*
3. *Create an algorithm for treatment of acute ischemic priapism.*
4. *What is the single best test for diagnosis of testis torsion?*
5. *The disruption of which fascial layer determines the route of extravasation of urine and/or blood following penile fracture?*

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## CHAPTER 10

# Urinary and Genital Trauma

Robert C. Kovell, MD • Jonathan L. Wright, MD, MS, FACS • Hunter Wessells, MD, FACS

## Introduction

Trauma remains the leading cause of death among young persons, and disability far exceeds mortality. Injuries are responsible for 8% of global mortality and 13% of global disability adjusted life years. One out of every 14 deaths in the United States is the result of trauma, and genitourinary injuries occur in approximately 10% of all trauma cases. Whereas kidney injuries cause acute hemorrhage and can be immediately life threatening, lower urinary tract and genital trauma may lead to lifelong disability and impaired quality of life.

## Kidney Injuries

Renal injuries, occurring in 1% to 5% of all trauma patients, are the most commonly observed genitourinary injuries. Advances in radiographic imaging, trauma care, and endovascular modalities have allowed significantly more renal traumas to be managed nonoperatively.

### INITIAL EVALUATION

After stabilization, gross inspection of the urine and urinalysis should be performed because hematuria is often an early indicator of renal trauma. **Any trauma patient presenting with hematuria must be evaluated for renal injury** (Figure 10-1). **However, the degree of hematuria correlates poorly with renal injury severity. Patients with renal artery thrombosis, ureteropelvic junction (UPJ) disruption, or renal pedicle avulsion may not have hematuria. A high degree of suspicion for renal trauma is required for patients who do not meet the hematuria criteria for imaging but who have experienced a fall from a height, a high-speed motor**

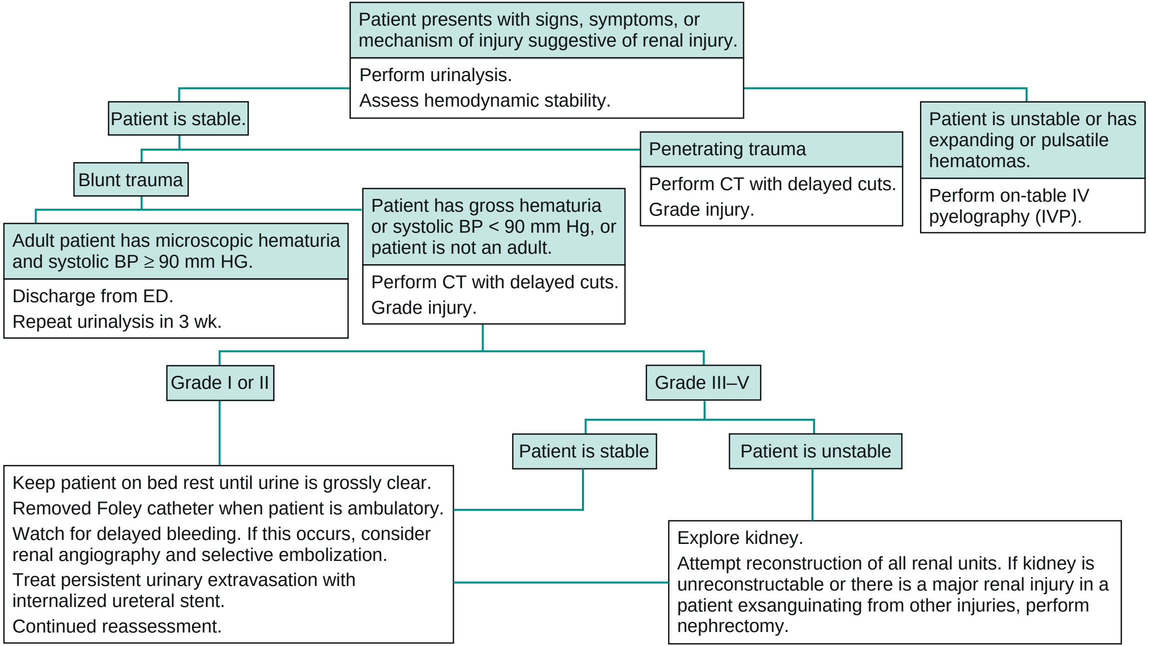

Patient presents with signs, symptoms, or mechanism of injury suggestive of renal injury.
Perform urinalysis.
Assess hemodynamic stability.
Patient is stable.
Patient is unstable or has expanding or pulsatile hematomas.
Perform on-table IV pyelography (IVP).
Penetrating trauma
Perform CT with delayed cuts.
Grade injury.
Blunt trauma
Adult patient has microscopic hematuria and systolic BP ≥ 90 mm HG.
Discharge from ED.
Repeat urinalysis in 3 wk.
Patient has gross hematuria or systolic BP < 90 mm Hg, or patient is not an adult.
Perform CT with delayed cuts.
Grade injury.
Grade I or II
Grade III–V
Patient is stable
Patient is unstable
Keep patient on bed rest until urine is grossly clear.
Removed Foley catheter when patient is ambulatory.
Watch for delayed bleeding. If this occurs, consider renal angiography and selective embolization.
Treat persistent urinary extravasation with internalized ureteral stent.
Continued reassessment.
Explore kidney.
Attempt reconstruction of all renal units. If kidney is unreconstructable or there is a major renal injury in a patient exsanguinating from other injuries, perform nephrectomy.

**FIGURE 10-1 Algorithm for evaluation and management of renal trauma.** (Modified from Wessells H: Injuries to the urogenital tract. In Souba WW, Fink MP, Jurkovich GJ, et al, editors: *ACS surgery: principles and practice,* New York, 2005, WebMD.)

**accident, or a direct blow to the flank. Patients with preexisting renal abnormalities are also at higher risk for traumatic renal injury.**

Hemodynamically stable patients with suspected renal injury and clinical indications such as blunt trauma with gross hematuria, microscopic hematuria associated with shock, rapid deceleration injuries, major associated injuries, or penetrating trauma to the abdomen, flank, or lower thorax should undergo prompt imaging. **Stable patients with microscopic hematuria and no reported hypotension can be observed clinically without renal imaging.**

For most renal trauma patients, **the imaging modality of choice is contrast-enhanced computed tomography** (CT) **to identify active arterial bleeding and parenchymal lacerations followed by a 10- to 15-minute delayed excretory phase to identify urinary contrast extravasation.** Hemodynamically unstable patients often require emergent stabilization and/or laparotomy. If the patient requires immediate laparotomy, on-table, one-shot intravenous urography (IVU) can provide useful information (see Management section). Angiography may be useful where selective embolization is considered.

## CLASSIFICATION

The American Association for the Surgery of Trauma (AAST) Organ Injury Scale is widely used to classify blunt and penetrating renal injuries based on either direct operative exploration or CT scan appearance (Figure 10-2). Multiple studies have shown that increasing AAST score correlates with increasing morbidity (need for nephrectomy, renorrhaphy, dialysis) and mortality (Tables 10-1 and 10-2).

## MANAGEMENT

Increasingly, renal trauma management is nonoperative with multiple series showing successful renal preservation despite high-grade injury. Nonoperative therapy has a low failure rate and a lower rate of nephrectomy than immediate operative management. **The absolute indications for operative exploration in renal trauma include hemodynamic instability, life-threatening hemorrhage, pedicle avulsion, or an expanding, pulsatile, or uncontained retroperitoneal hematoma.** Complications that once required open surgery can often be managed nonsurgically: Active

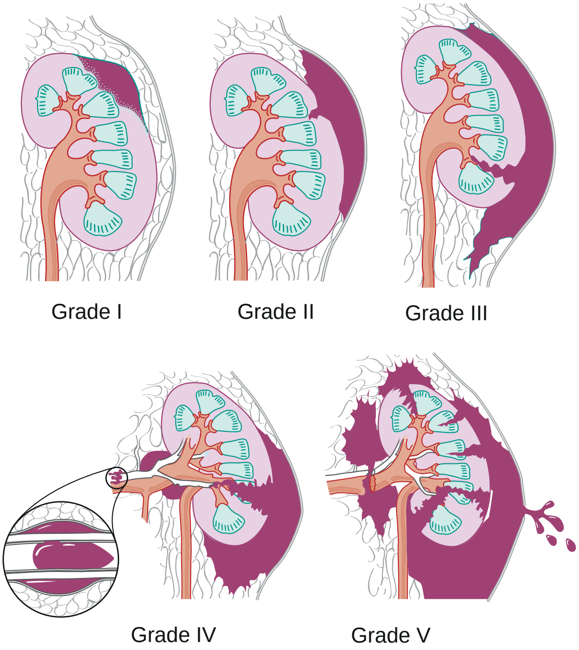

Grade I
Grade II
Grade III
Grade IV
Grade V

**FIGURE 10-2 AAST organ injury scale for the kidney.** (From McAninch JW, Santucci RA: Genitourinary trauma. In Walsh PC, et al, editors: *Campbell's urology*, ed 8. St. Louis, 2002, WB Saunders.)

arterial bleeding and arterial pseudoaneurysms are controlled with selective angioembolization, and perinephric abscesses and urinomas can be treated with percutaneous drainage and/or indwelling ureteral stents.

Currently, 20% to 50% of all penetrating renal injuries and fewer than 10% of blunt injuries require operative management. **Grade I-III renal injuries, regardless of mechanism, are generally managed with observation alone. In hemodynamically stable patients, many grade IV (Figures 10-3 and 10-4) and selected grade V injuries can be managed nonoperatively with close monitoring, hydration, serial hematocrit measurement, and repeat imaging with a high success rate. Patients are kept on bed rest until the urine is grossly clear.** Foley catheter drainage is necessary only until other injuries are stable and the patient can void spontaneously.

TABLE 10-1 **Multivariate Predictors of Morbidity and Mortality for Blunt Renal Trauma***

| | Nephrectomy (n=289) | Dialysis (n=33) | Death (n=709) |
|---|---|---|---|
| AAST I | Reference group | Reference group | Reference group |
| AAST II | 2.5 (1.0-6.2) | 1.5 (0.41-5.6) | 0.95 (0.65-1.4) |
| AAST III | 12 (5.6-25) | 1.3 (0.45-4.6) | 1.3 (0.90-2.0) |
| AAST IV | 64 (34-120) | 3.7 (1.2-11) | 1.4 (0.97-2.0) |
| AAST V | 127 (68-236) | 4.7 (1.4-16) | 1.9 (1.3-2.7) |
| Bowel surgery | 2.3 (1.8-2.9) | 3.9 (1.5-10) | |
| Spleen surgery | 2.2 (1.8-2.8) | | 2.1 (1.4-3.0) |
| Liver surgery | 1.5 (1.2-2.0) | | |
| ISS > 15 | | | 2.8 (1.4-5.6) |
| ISS > 24 | | | 3.0 (2.0-4.4) |
| ISS > 47 | | | 1.7 (1.3-2.3) |
| SBP < 90 | | | 2.0 (1.5-2.6) |
| Abd AIS > 3 | | 5.3 (1.9-15) | |
| Head AIS > 3 | | | 2.5 (1.9-3.4) |
| Age > 40 years | 1.3 (1.0-1.5) | 4.0 (2.2-7.3) | 2.0 (1.6-2.4) |

*Blank cells indicate the parameter was not an independent predictor for that particular outcome.

AAST, *American Association for the Surgery of Trauma;* AIS, *Abbreviated Injury Scale;* ISS, *injury severity score;* SBP, *systolic blood pressure.*

Thrombosis of the renal artery or its branches is treated nonoperatively unless the contralateral kidney is absent or severely injured, in which case emergency revascularization is indicated.

Renal exploration often leads to nephrectomy, either as damage control in the exsanguinating patient or unnecessarily by surgeons unfamiliar with renal reconstructive techniques. Other predictors of nephrectomy include the AAST renal injury scale, the Injury Severity Score (ISS), transfusion requirements, and operations on other intraabdominal organs.

## Operative Management

A significant number of patients with a penetrating injury and a minority of those with blunt trauma require immediate laparotomy before radiographic evaluation. If a major renal injury is suspected based on the size of the perinephric hematoma, a one-shot intraoperative IVU is recommended before renal

TABLE 10-2 **Multivariate Predictors of Morbidity and Mortality for Penetrating Renal Trauma***

| | Nephrectomy (n=333) | Dialysis (n=6) | Death (n=249) |
|---|---|---|---|
| AAST I | Reference group | | |
| AAST II | 1.1 (0.3-3.7) | | |
| AAST III | 7.7 (3.2-18) | | |
| AAST IV | 25 (10-63) | | |
| AAST V | 31 (12-82) | | |
| Firearm injury | 25 (10-63) | | |
| Bowel surgery | 31 (12-82) | | |
| Spleen surgery | | | 0.42 (0.22-0.81) |
| Liver surgery | | | 0.44 (0.23-0.87) |
| ISS>24 | | | 4.6 (2.27-9.2) |
| SBP<90 | | | 2.8 (1.6-4.9) |

*Blank cells indicate the parameter was not an independent predictor for that particular outcome. There were too few patients with dialysis (n=6) for a meaningful prediction model.

AAST, *American Association for the Surgery of Trauma;* ISS, *injury severity score;* SBP, *systolic blood pressure.*

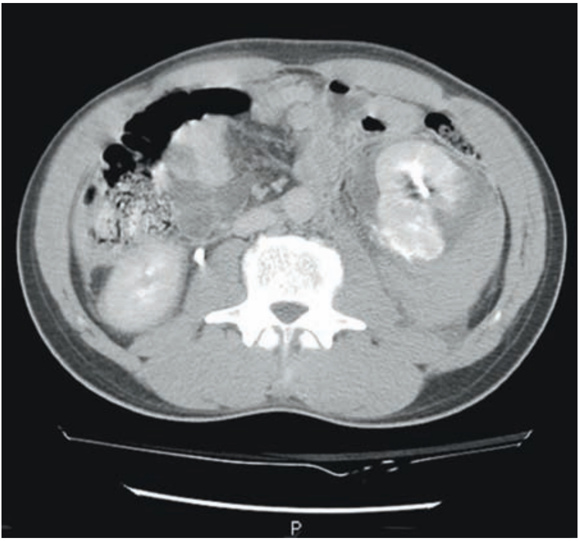


FIGURE 10-3 Grade IV renal laceration with urinary extravasation and perinephric hematoma.

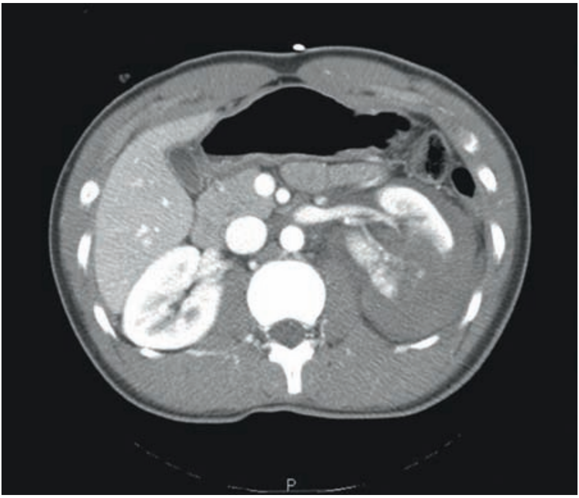


FIGURE 10-4 Left grade IV renal injury with deep laceration, extensive parenchymal damage, and large perinephric hematoma. Excretory imaging would be needed to further assess the integrity of the collecting system.

exploration to confirm the presence of a contralateral functioning kidney and potentially to rule out major injury. A 2 mL/kg bolus of contrast material is administered 10 minutes before obtaining a single plain abdominal film. Abnormalities of the affected kidney, including poor visualization, require operative exploration.

**In the critically ill patient with multiple injuries, renal exploration is indicated if a pulsatile or expanding hematoma is present, in which case a rapid nephrectomy is often necessary. Less severe injuries can be managed with renorrhaphy, partial nephrectomy, perinephric drains, embolization, and damage control techniques described later.** In most cases, renal reconstruction and salvage is possible; however, if the patient is unstable and has a normal contralateral kidney, rapid nephrectomy may be prudent. Selective renal embolization via angiography may be considered when no other injury requires immediate surgical exploration and conservative measures have failed to control hemorrhage. This strategy has demonstrated high success rates and low complication rates for grade IV injuries but often fails for grade V injuries.

**Operative management of grade III and IV injuries consists of hemorrhage control first, followed by repair of the collecting system and parenchymal closure. In blunt grade V injuries requiring exploration, nephrectomy is almost always the preferred treatment except in solitary kidneys or bilateral renal injuries.**

**A midline transabdominal incision permits exploration of the kidneys, allows complete inspection of the intraabdominal contents, and provides optimal access to the renal hilum. Isolation of the renal artery and vein is recommended and should be achieved by opening the posterior peritoneum medial to the inferior mesenteric vein or by reflecting the ipsilateral colon (provided that the perinephric hematoma is left undisturbed).** Early vascular control appears to increase the rate of renal salvage. Once the renal vessels are isolated, Gerota fascia is opened. If massive bleeding occurs when the hematoma is entered, Rummel tourniquets or vascular clamps are applied to the renal artery and vein.

The principles of renal reconstruction include complete exposure, debridement of devitalized tissue, achievement of hemostasis, watertight collecting-system closure, coverage of the defect, and drainage. Bleeding points must be controlled using figure of eight sutures of fine absorbable monofilament.

Once hemostasis is satisfactory, collecting-system openings are closed with 4-0 absorbable sutures. The defect in the parenchyma can be filled with folded absorbable gelatin sponges as the capsule is closed over the bolsters. For polar injuries, partial nephrectomy can be considered instead. The addition of hemostatic agents such as Floseal may also be helpful. If the renal capsule has been destroyed, coverage options include an omental or perinephric fat flap, a patch of polyglycolic acid or peritoneum, or an entire sac of polyglycolic acid wrapped around the kidney, with the parenchymal edges kept well apposed. Gerota fascia is not reapproximated. Closed-suction drainage of the ipsilateral retroperitoneum is recommended. Internalized stents are reserved for complex injuries (e.g., large lacerations of the renal pelvis or the UPJ).

Prompt nephrectomy is generally advised in the rare case of major renovascular injuries because salvage rates after renal vascular reconstruction are low. In unstable patients, damage control with renal packing and planned reevaluation in 24 hours can also be considered in an attempt to avoid nephrectomy.

## COMPLICATIONS

The risk of complications increases with each increasing grade of renal injury. The most significant early complications are delayed bleeding, infection, and urinary leakage. For grade IV-V injuries managed nonoperatively, follow-up imaging at 48 to 96 hours after the initial scan minimizes the risk of missed complications. For lower grade injuries, repeat imaging can be safely omitted unless signs of infection, decreasing hematocrit, persistent hematuria, and persistent flank plan are present.

**Urinary extravasation** can often be managed with systemic antibiotics and close observation. **If the extravasation persists, internalized ureteral stenting is indicated, especially in the setting of obstruction or infection.** The urinary bladder should be drained with a Foley catheter until any extravasation resolves, which can take days to weeks. Ultrasonography is useful for following such collections and for reducing the patient's radiation exposure. If the perinephric fluid collection is large enough to compress the ureter or becomes infected, additional percutaneous drainage is required.

**Delayed bleeding** is a rare, life-threatening complication of major lacerations. Pseudoaneurysm formation and arteriovenous malformation (AVM) are the most common causes of delayed bleeding and usually occur within 2 weeks post injury. **Selective arterial embolization is an effective treatment in most instances.**

**Hypertension** is a rare late complication of renal injuries that is usually renin mediated from an ischemic segment of parenchyma. This occurs in about 5% of renal trauma patients. Etiologies include renal arterial injury leading to stenosis, extrinsic compression from urinary or blood extravasation (Page kidney), an ischemic parenchymal fragment, or arteriovenous fistula. Angiography, decortication, excision of the nonperfused segment, or nephrectomy may be required in these rare cases. Long-term blood pressure monitoring is often necessary.

# Ureteral Injuries

## INITIAL EVALUATION

Most ureteral injuries are iatrogenic, primarily resulting from gynecologic, general surgical, or urologic procedures. External ureteral trauma is relatively rare, accounting for approximately 1% of all genitourinary injuries. **Ureteral injuries more commonly**

**occur with penetrating trauma and deceleration injuries, and patients usually have multiple associated abdominal injuries.** Patients with ureteral injuries have a mortality rate of 6% to 10% as a result of associated injuries, which reflect the penetrating trauma and high-velocity motor vehicle crash mechanisms. A high index of suspicion is thus necessary to prevent a delay in diagnosis with resultant late consequences such as urinoma, sepsis, stricture, and nephrectomy.

**Hematuria may be absent in 25% to 45% of patients with ureteral injury,** which contributes to a delay in diagnosis. **Stable patients with suspected ureteral injuries should undergo CT with intravenous contrast and delayed images to evaluate for urinary extravasation.** If further clinical information is needed, **retrograde pyeloureterography can be used** to more accurately define the extent of the injury (Figure 10-5). Ureteral injury at the UPJ or near the iliac vessels can occur after severe deceleration

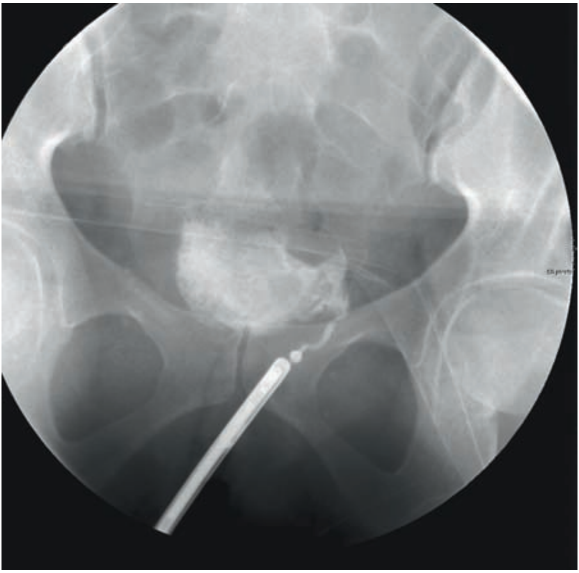


FIGURE 10-5 Left retrograde ureterogram demonstrating a distal ureteral injury. Extensive extravasation of contrast is seen approximately 1-2 cm proximal to the left ureterovesical junction. (Courtesy of Dr. Parvati Ramchandani, University of Pennsylvania Health System)

or ejection from a high-speed vehicle, particularly in children, in whom the hyperextensibility of the spine leads to UPJ avulsion. Medial or circumrenal contrast extravasation on CT scan should raise suspicion for UPJ disruption.

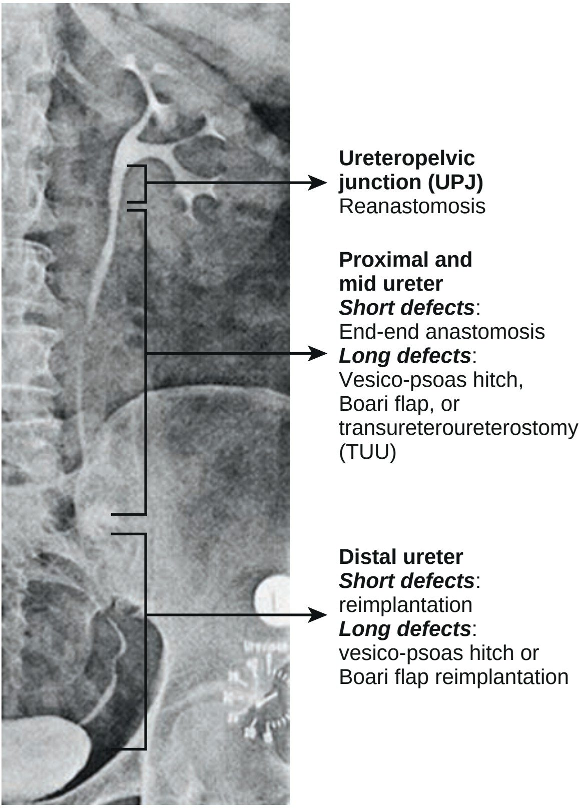
Unstable patients taken to the operating room without imaging can be evaluated intraoperatively with a one-shot IVU, although this proves nondiagnostic for ureteral injuries in 33% to 100% of cases. **Indications for exploration include a retroperitoneal hematoma and a projectile trajectory that put the ureter at risk.** In meta-analysis from 16 large trauma centers, **89% of ureteral injuries were identified at the time of exploratory laparotomy.** Gentle instillation of 1-2 mL of methylene blue or indigo carmine into the collecting system may help to identify sites of laceration or avulsion.

## MANAGEMENT

Management depends on the degree of injury, the location of the ureteral injury (Figure 10-6), and the timing of diagnosis. **Injuries recognized initially should be surgically repaired. If a patient is not stable, ligation of the ureter and nephrostomy tube drainage or exteriorization of a ureteral stent allows elective repair at a later time.** If diagnosis is delayed, percutaneous nephrostomy and ureteral stenting, followed by delayed definitive management, avoids the risk of nephrectomy associated with operative exploration. **Nephrectomy should be considered in cases where concomitant vascular repair using prosthetic material may be complicated by urine leakage.**

### Operative Management

The principles of ureteral reconstruction include debridement of devitalized tissue, sparing ureteral adventitia, a spatulated tension-free anastomosis, watertight closure with absorbable suture, internal stenting, coverage of the repair, and drainage. **Minor contusions can be managed with stent placement. Larger ureteral contusions often lead to stricture or delayed breakdown as a result of microvascular injury; in such cases excision and ureteroureterostomy should be considered. Partial transections may be closed primarily. Gunshot ureteral injuries usually require debridement** to reduce the risk of blast-induced microvascular damage, **whereas stab wounds do not.** However, in all cases, mobilization of the ureter should be limited to preserve blood supply. All repairs should be performed with interrupted 5-0 or



**Ureteropelvic junction (UPJ)**
Reanastomosis

**Proximal and mid ureter**
***Short defects***:
End-end anastomosis
***Long defects***:
Vesico-psoas hitch,
Boari flap, or
transureteroureterostomy
(TUU)

**Distal ureter**
***Short defects***:
reimplantation
***Long defects***:
vesico-psoas hitch or
Boari flap reimplantation

FIGURE 10-6 Management of ureteral injury based on segment of ureter injured. (From Kuan J, Routt ML, Wessells H: Genitourinary and pelvic trauma. In Mulholland, MW, Lillemoe KD, Doherty GM, et al, editors: *Greenfield's surgery: scientific principles and practice*, ed 4, Philadelphia, 2006, Lippincott, Williams & Wilkins.)

6-0 absorbable sutures over an internalized or externalized stent. Closed-suction retroperitoneal drainage and Foley catheter decompression of the bladder should be utilized.

## Upper Ureter

**Disruption of the upper ureter or the UPJ is repaired with primary anastomosis of the ureter to the renal pelvis or, when necessary, ureterocalycostomy. Proximal ureteral injuries can**

**be handled by ureteroureterostomy when possible.** The ureteral ends are spatulated on opposite sides for the anastomosis. In cases of associated colonic, duodenal, or pancreatic injuries, an omentum flap or retroperitoneal fat should be used, when possible, as an additional layer of coverage. Renal mobilization can be utilized if needed. Alternatively, transureteroureterostomy, bowel interposition, or renal autotransplant may be required for an elongated segment of damaged ureter. The latter procedures are not indicated in the acute injury setting.

### Mid Ureter

**Short ureteral injuries can often be repaired via ureteroureterostomy**. Alternatively, a transureteroureterostomy or a Boari flap with neoureterocystostomy can be performed. If a flap is employed, the base of the flap should be approximately four times the width of the ureter. Regardless of the type of repair performed, a stent (5-French pediatric feeding tube or single-J or double-J ureteral stent) should be placed across the anastomosis and be brought through the bladder.

### Distal Ureter

**Injuries below the pelvic brim are best managed with ureteral reimplantation into the bladder**. The distal stump is ligated, and after the anterior bladder wall is opened, the spatulated end of the ureter is brought through a new hiatus on the back wall of the bladder. Larger defects can be bridged with a vesico-psoas hitch after mobilizing the contralateral bladder pedicle. In rare cases in which complex bladder or pelvic vascular injuries preclude extensive pelvic dissection, a transureteroureterostomy may be performed.

## COMPLICATIONS

Fistula formation because of distal obstruction or ureteral necrosis is rare. Fistulas should be managed with antegrade or retrograde drainage of the collecting system with percutaneous or endoscopic techniques. Drainage of periureteral fluid collections is essential. If recognition of an injury or a complication is delayed, reconstruction should be deferred for at least 3 to 6 months until all inflammation has subsided.

# Injuries to the Bladder

## INITIAL EVALUATION

Bladder injury occurs most commonly in association with a pelvic fracture. Whereas 70% to 97% of bladder ruptures have an associated pelvic fracture, only 5% to 10% of pelvic fractures have an associated bladder rupture. Additionally, patients undergoing gynecologic, urologic, and general surgical procedures are at risk for iatrogenic bladder injury.

Figure 10-7 illustrates an algorithm for evaluation and management of bladder trauma. **CT cystography has become the modality of choice for identifying bladder rupture** (Figures 10-8 and 10-9). Cystography requires adequate distension of the bladder (generally with greater than 350 cc) to obtain accurate results. The sensitivity and specificity of CT cystography at one large trauma center were 95% and 100%, respectively. **Conventional fluoroscopic cystography (85% to 100% accuracy) is an acceptable alternative but requires scout and postdrainage films.** Routine IVU or CT urography cannot reliably exclude bladder injury.

**The indications for cystography at our institution include blunt trauma with gross hematuria in the presence of free abdominal fluid on CT, blunt trauma with a pelvic fracture and greater than 30 red blood cells (RBCs) per high-power field (HPF), and stable penetrating trauma with any degree of hematuria and an injury to the pelvis.** Hematuria occurs in almost all cases of significant bladder injury. Specific fracture patterns have been identified as predictors of bladder injury, namely pubic symphyseal diastasis greater than 1 cm and obturator ring fracture with greater than 1 cm displacement.

Bladder injuries are classified as either extraperitoneal or intraperitoneal. The distinction can be made on CT or conventional cystography, and the classification is important because of different management strategies.

## MANAGEMENT

### Extraperitoneal Injuries

Blunt, extraperitoneal bladder injuries have generally been managed nonoperatively with 7–14 days of large-bore catheter drainage. **Contraindications to a nonoperative approach include penetrating injuries, urinary tract infection (UTI), pelvic**

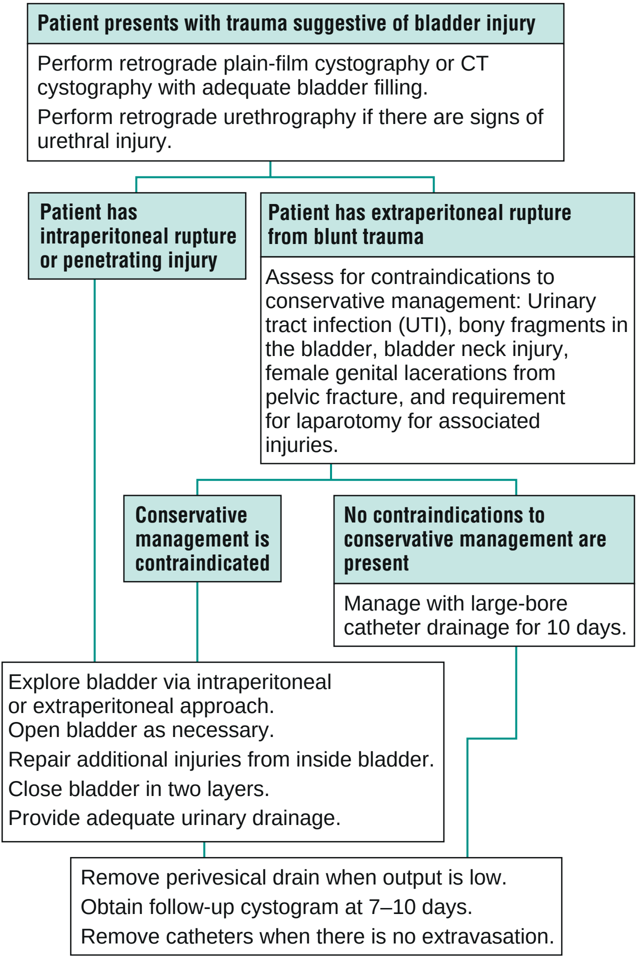

Patient presents with trauma suggestive of bladder injury
Perform retrograde plain-film cystography or CT cystography with adequate bladder filling.
Perform retrograde urethrography if there are signs of urethral injury.
Patient has intraperitoneal rupture or penetrating injury
Patient has extraperitoneal rupture from blunt trauma
Assess for contraindications to conservative management: Urinary tract infection (UTI), bony fragments in the bladder, bladder neck injury, female genital lacerations from pelvic fracture, and requirement for laparotomy for associated injuries.
Conservative management is contraindicated
No contraindications to conservative management are present
Manage with large-bore catheter drainage for 10 days.
Explore bladder via intraperitoneal or extraperitoneal approach.
Open bladder as necessary.
Repair additional injuries from inside bladder.
Close bladder in two layers.
Provide adequate urinary drainage.
Remove perivesical drain when output is low.
Obtain follow-up cystogram at 7–10 days.
Remove catheters when there is no extravasation.

FIGURE 10-7 Algorithm for evaluation and management of bladder trauma. (From Wessells H: Injuries to the urogenital tract. In Souba WW, Fink MP, Jurkovich GJ, et al, editors: *ACS surgery: principles and practice*, New York, 2005, WebMD.)

**fractures requiring internal fixation of the pubis, the presence of bony fragments in the bladder, bladder neck injury, rectal injury, and female genital lacerations associated with pelvic fracture.** In patients undergoing exploration, the bladder can be

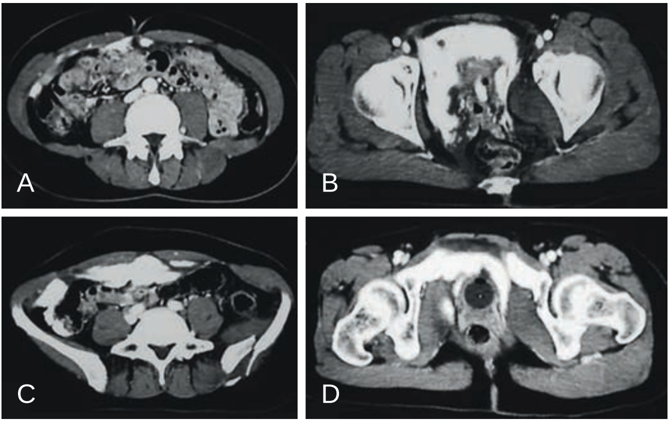


FIGURE 10-8 CT cystogram images of extraperitoneal bladder rupture. **A,** Note contrast tracking to the umbilicus. **B,** Contrast tracking lateral to colon, not to be confused with contrast outlining loops of small intestine in an intraperitoneal injury. **C.** "Molar tooth" configuration of contrast surrounding the bladder in the upper space of Retzius. **D,** Contrast surrounding the lower bladder and bladder neck region.

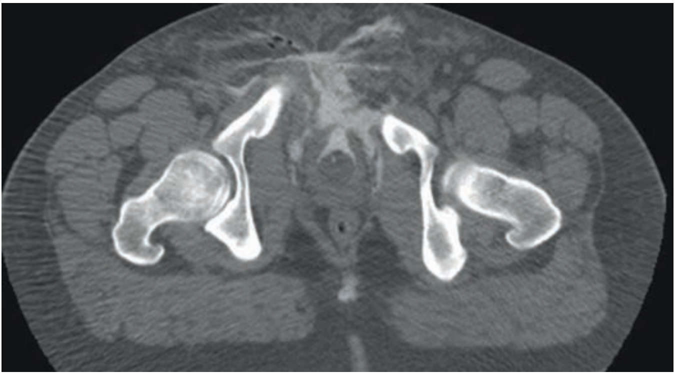


FIGURE 10-9 Traumatic injury to the bladder extending though the bladder neck as seen on CT cystogram. Note contrast extravasation into the extraperitoneal space anterior to the inflated Foley balloon.

approached extraperitoneally because the majority of injuries associated with pelvic fractures are anteriorly located, small in size, and easily managed without an extensive bladder exposure. **Any significant bladder injury from penetrating trauma should be explored.**

### Intraperitoneal Injuries

Intraperitoneal bladder rupture due to trauma requires exploration and repair due to the large size and location at the dome. **A complete intravesical examination excludes a concomitant extraperitoneal injury, which can occur in 8% of cases.** The ureteral orifices and bladder neck should be inspected. Additional lacerations found within the bladder are closed with 3-0 absorbable sutures, approximating the detrusor and mucosa in one layer and providing hemostasis. The primary laceration, usually at the dome, is closed with two layers of continuous 2-0 slowly absorbable sutures; a 20-French urethral catheter should be placed to maximize drainage. Suprapubic catheters are not indicated unless an unrepaired urethral injury is present or severe hematuria resulting from coagulopathy or extensive injuries necessitates additional drainage to allow for clot irrigation and additional bladder decompression. A closed-suction drain near the bladder closure is recommended and can be removed after 2 to 3 days unless the creatinine level in the drainage fluid indicates urinary leakage.

## COMPLICATIONS

After open repair or a trial of nonoperative management, cystography should be performed prior to catheter removal. **If extravasation persists, the catheter should be left in place and cystography repeated at appropriate intervals until healing occurs.** Complications of bladder injury are primarily due to a delay in diagnosis leading to azotemia, ascites, and sepsis. Bladder neck injury, if not identified and repaired, may result in an incompetent proximal sphincteric mechanism and subsequent incontinence. Persistent leakage after repair is rare and usually responds to catheter drainage. Persistent extravasation suggests catheter obstruction, bony fragments, or ischemic complications of injury or embolization.

## Urethral Injuries

**Urethral injuries occur in up to 5% of males and 6% of females with pelvic fractures.** In men, traumatic urethral injury usually occurs in the posterior urethra, primarily at the prostatomembranous junction. Approximately 10% to 20% of patients will have concomitant bladder injuries. Characteristics of patients with urethral injury include age younger than 40 years; multiple associated injuries to the head, abdomen, and chest; involvement in motor vehicle crashes; and high injury severity scores. Figure 10-10 illustrates an algorithm for the evaluation and management of urethral trauma.

### MECHANISMS

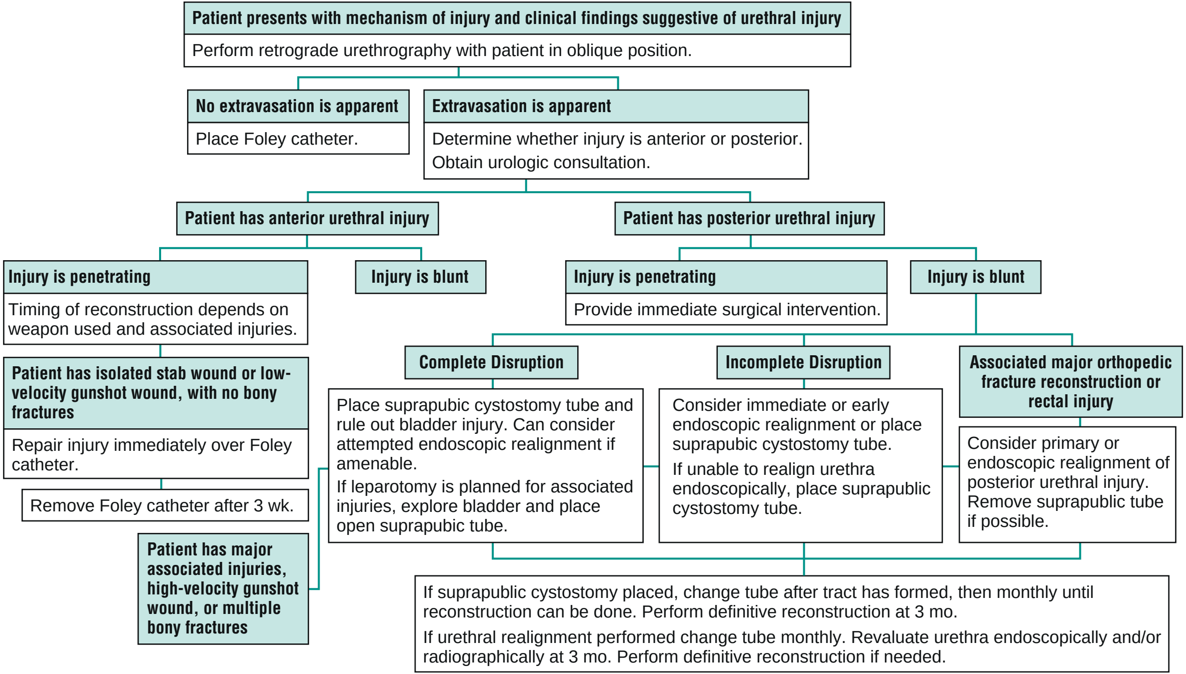
Pelvic fractures are the most common cause of posterior urethral injury in males. The classic injury is a distraction injury at the bulbomembranous or prostatomembranous junction. Variations occur, including complete and partial disruption, and the tears can occur above, below, or through the urogenital diaphragm (Figure 10-11). Displaced fractures of the pubis, pubic rami, and unstable pelvic fractures are associated with urethral injury in men.

The female urethra is rarely injured, but a review from our institution showed that urethral and bladder neck injuries were always associated with pelvic fracture. Longitudinal tears may originate in the bladder neck, whereas avulsion type injuries probably share similar mechanisms with male type distractions of the membranous urethra. Vulvar edema or blood at the vaginal introitus should raise suspicion of a urethral injury.

Anterior urethral (penile and bulbar urethral) injuries in men are rarely caused by pelvic fractures. They are most commonly caused by straddle injury, in which the corpus spongiosum is crushed against the pubic symphysis. Other mechanisms include perineal trauma, penile fracture, amputation, and penetrating injuries to the genitalia.

### INITIAL EVALUATION

Signs and symptoms of urethral injury are variable, and thus careful history, physical examination, and radiographic imaging are critical to determine the location, nature, and extent of injury. Inability to void and painful attempts to void suggest urethral injury. Blood at the urethral meatus, the classic sign of injury to



**Patient presents with mechanism of injury and clinical findings suggestive of urethral injury**

Perform retrograde urethrography with patient in oblique position.

**No extravasation is apparent**

Place Foley catheter.

**Extravasation is apparent**

Determine whether injury is anterior or posterior.

Obtain urologic consultation.

**Patient has anterior urethral injury**

**Injury is penetrating**

Timing of reconstruction depends on weapon used and associated injuries.

**Patient has isolated stab wound or low-velocity gunshot wound, with no bony fractures**

Repair injury immediately over Foley catheter.

Remove Foley catheter after 3 wk.

**Patient has major associated injuries, high-velocity gunshot wound, or multiple bony fractures**

**Injury is blunt**

**Patient has posterior urethral injury**

**Injury is penetrating**

Provide immediate surgical intervention.

**Injury is blunt**

**Complete Disruption**

Place suprapubic cystostomy tube and rule out bladder injury. Can consider attempted endoscopic realignment if amenable.

If leparotomy is planned for associated injuries, explore bladder and place open suprapubic tube.

**Incomplete Disruption**

Consider immediate or early endoscopic realignment or place suprapubic cystostomy tube.

If unable to realign urethra endoscopically, place suprapubic cystostomy tube.

**Associated major orthopedic fracture reconstruction or rectal injury**

Consider primary or endoscopic realignment of posterior urethral injury. Remove suprapubic tube if possible.

If suprapubic cystostomy placed, change tube after tract has formed, then monthly until reconstruction can be done. Perform definitive reconstruction at 3 mo.

If urethral realignment performed change tube monthly. Revaluate urethra endoscopically and/or radiographically at 3 mo. Perform definitive reconstruction if needed.

FIGURE 10-10 **Algorithm for evaluation and management of urethral trauma.** (Modified from Wessels H: Injuries to the urogenital tract. In Souba WW, Fink MP, Jurkovich GJ, et al, editors: *ACS surgery: principles and practice*, New York, 2005, WebMD.)

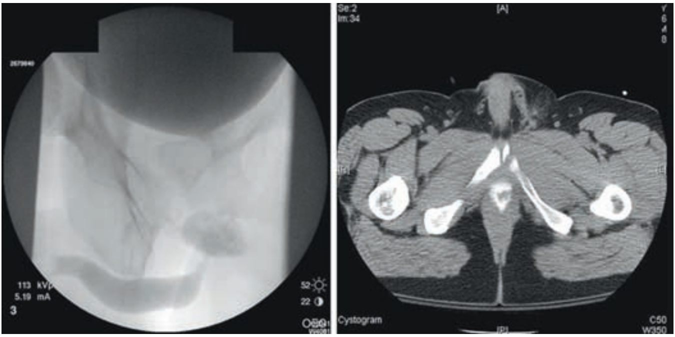


FIGURE 10-11 Retrograde urethrogram *(left panel)* and CT cystogram *(right panel)* of urethral disruption demonstrating contrast extravasation. The bladder is full in the left panel because of prior CT scan.

the urethra, occurs in 37% to 93% of urethral injuries and indicates that imaging should be performed immediately. Other signs include a palpable bladder, butterfly perineal hematoma, and high-riding prostate, although these are significantly less reliable. Gentle attempts to pass a catheter have not been shown to convert partial urethral tears into complete transections.

In female patients, many urethral and bladder neck injuries are missed and only detected at the time of operative exploration. Therefore the presence of vaginal bleeding or labial swelling should prompt urgent speculum examination, under anesthesia if necessary, and consideration for imaging or cystoscopy.

**Imaging of the urethra with retrograde urethrography in males and cystography in females remains the recommended initial evaluation for suspected urethral injury. The sensitivity and specificity of urethrography are high in men. Conversely, cystography may miss some female urethral or bladder neck injuries. Thus in cases of suspected injury not clearly defined on radiographic imaging, we advocate cystourethroscopy as an adjunctive diagnostic measure.**

## MANAGEMENT

### Posterior Urethra

**Suprapubic cystostomy remains standard management of pelvic fracture urethral injury (PFUI) and straddle injuries to the bulbar urethra.** Percutaneous placement of the tube under fluoroscopic guidance or open placement through a small infraumbilical incision allows temporary urinary diversion for initial stabilization and evaluation of the patient. Cystography can be performed via the suprapubic tube to rule out bladder injury. Straddle injuries must be treated with diversion unless the disruption is only partial and allows safe passage of a guide wire or catheter under fluoroscopic guidance. Suprapubic cystostomy is recommended for penetrating trauma to the urethra if the injuries were caused by high-velocity weapons and are characterized by extensive tissue loss or if serious associated injuries are present.

**Urethral realignment without sutured repair may be considered as an alternative for PFUI.** Early endoscopic realignment can be undertaken 3 to 7 days after the initial injury and may decrease stricture rates, allow future endoscopic management, and possibly simplify formal urethroplasty if required. Prolonged attempts at endoscopic realignment should not be attempted because this may increase the risk of pelvic hematoma or infection. A relative indication for realignment of PFUI is open reduction and internal fixation of anterior pelvic ring fractures. Realignment allows early removal of suprapubic cystostomy tubes from the orthopedic field, although evidence that suprapubic tubes increase complications in these cases is lacking.

**The presence of bladder neck or rectal injuries indicates the need for immediate management and early realignment of the urethral injury. Female urethral injuries in combination with bladder neck, rectal, or vaginal injuries also warrant early surgical intervention.** Evacuation of the pelvic hematoma, irrigation, placement of drains, and primary realignment (men) or repair (women) of the urethra are strongly recommended.

## Anterior Urethra

**Penetrating anterior urethral injuries in men are best treated with immediate repair. Exceptions to this rule include high-velocity gunshots wounds or injuries associated with extensive tissue destruction.** These injuries should always be treated with urinary diversion and delayed repair. Patients experiencing blunt trauma to the anterior urethra, especially straddle-type crush injury to the bulbar urethra, are generally managed with suprapubic cystostomy and delayed imaging studies with repair as needed.

**Immediate reconstruction is preferred for penetrating injuries of the bulbar and penile urethra and for urethral injuries associated**

**with penile fracture.** For these partial or complete transections without major tissue loss, primary repair is associated with a lower stricture rate than simple realignment. Wounds accompanied by major tissue loss and defects larger than 1.0-1.5 cm (e.g., grade V injuries) or complicating associated injuries are best treated with suprapubic cystostomy diversion and subsequent reconstruction at a tertiary referral center.

### Postintervention Care

After early realignment of urethral injuries, the urethral catheter is left in place for 6 weeks, at which time a pericatheter retrograde urethrogram is obtained, with the expectation that any extravasation will have resolved. The urethral catheter should remain in place for 1 to 3 weeks after immediate surgical repair of the anterior urethra, at which time contrast voiding cystourethrography is obtained. If extravasation is present, continued catheter drainage for another 1 to 2 weeks is needed before repeating the study.

If the patient initially underwent diversion with suprapubic cystostomy, the tube should be changed after a tract has formed and monthly until reconstruction can be performed, generally 3 to 6 months after the injury. Stricture formation or complete distraction defect of the urethra may be the final result of this approach. Subsequent radiographic studies will indicate whether secondary endoscopic or open procedures are needed.

After PFUI, erectile dysfunction (ED) will occur in 20% to 60% of patients and is primarily determined by the severity of the initial injury rather than the treatment selected. ED following trauma is usually neurogenic or vasculogenic in nature and may improve spontaneously up to 2 years following injury. After posterior reconstruction, urinary continence is achieved in 95% of all patents.

## Injuries to the Male External Genitalia

Genital injuries are significant because of their association with injuries to major pelvic and vascular organs and the potential for chronic disability. In civilians suffering genitourinary gunshot wounds, the scrotum will be affected in 21%, the testes in 12% and the penis in 8%, with upwards of 90% of these patients sustaining significant additional injuries. **Penetrating injuries to the**

**external genitalia have a high likelihood of associated injuries to the spermatic cord, testis, urinary bladder, urethra, rectum, and vascular structures of the iliac and femoral region.** General wound care principles include irrigation, debridement, and closure of all wound layers. Most lacerations of the genital skin can be closed primarily due to the excellent blood supply. In the following sections we discuss the presentation, evaluation and management of several common injuries to the external genitalia.

## PENILE INJURIES

The flaccidity of the penis limits the transfer of kinetic energy during trauma. In contrast, the fixed crura of the penis in relation to the pubic rami, are prone to blunt trauma from pelvic fracture or straddle injury. Firearms and missiles have enough kinetic energy to overcome the protective mechanisms of flaccidity.

## PENILE FRACTURE

The erect penis becomes more prone to injury: Missed intromission or manual attempts at detumescence can cause rupture of the tunica albuginea, known as a penile fracture. Acute bending and a popping sound followed by immediate detumescence of the penis and pain are characteristic of penile fracture. Penile swelling is usually limited by Buck fascia to the shaft of the penis causing the commonly seen “eggplant deformity.” A perineal butterfly hematoma extending up the abdomen can occur when Buck fascia has been traumatically ruptured. In these cases, Colles fascia contains the hematoma.

**Urethral injury occurs in 10% to 38% of penile fractures, and the integrity of the urethra should be investigated in all penile fractures.**

History and physical examination are usually enough to distinguish between subcutaneous hematoma and penile fracture. **Ancillary tests to detect penile fracture, such as ultrasonography and cavernosography, have unacceptably high false negative rates**, limiting their clinical applicability. Magnetic resonance imaging (MRI) is accurate at delineating tunical disruption and may be useful in atypical presentations when accessible. **Conservative management is not recommended and increases the risk of missed urethral injuries, prolonged hospitalization, penile curvature, and ED.**

## Operative Management

Exposure of the deep cavernosum and tunica albuginea can be achieved through a circumferential subcoronal incision via degloving, or for deeper wounds, a penoscrotal, infrapubic, or even perineal incision. Fracture injuries are usually 1-2 cm in length, ventrolateral, and distal to the suspensory ligament. The degloving incision generally works well for penile fractures and allows complete inspection of the urethra and cavernosa. **Flexible cystoscopy can be performed before catheter placement if urethral injury is suspected.** If urethral injury is discovered, it can be repaired concomitantly with low stricture rate.

After clearing clot and hematoma, we close the tunica albuginea with slowly absorbable, interrupted sutures in a transverse fashion to prevent narrowing of the corpora. Artificial erection may help in locating corporeal defects.

## PENETRATING TRAUMATIC PENILE INJURIES

Penetrating trauma to the penis causes associated injuries in up to 83% of patients. Urethral injury occurs in 20% to 50% of penile gunshot wounds. **Retrograde urethrography or cystoscopy should be strongly considered with all penetrating penile injuries,** especially when the clinical picture of mechanism suggests urethral involvement.

## Operative Management

Operative management includes prompt surgical exploration, copious irrigation, removal of foreign material, antibiotic coverage, and closure. Primary closure can be achieved in virtually all cases. We close the tunica albuginea in the same manner as for a fracture. Urethral injuries can be managed with standard protocols described above. Penetrating defects in the tunica albuginea may be so large as to preclude primary closure. In such instances, which are rare in civilian practice, off-the-shelf fascia, pericardium, or other collagen matrix-type products may be helpful.

Defects of glanular tissue do not preclude a good outcome: Debridement and trimming of skin edges to create a clean wound allow for closure of fairly large defects. Although the size of the glans may be reduced, its overall contour can usually be maintained.

Extensive irrigation is appropriate to remove any foreign material, including clothing, missile fragments, or pieces of bone, that may enter the deep structures of the penis and urinary tract. These must be actively sought in such cases and removed.

## PENILE AMPUTATION

A rare cause of penile injury is amputation. Penile amputation may be a manifestation of depressive and psychotic behavior, due to either mental illness or illicit drug abuse. In these cases, consider consultation with psychiatric specialists. Constriction rings can cause loss of superficial skin, deep urethral necrosis, or complete penile loss. When assault is the cause, appropriate police reporting is required.

**After penile amputation or self-mutilation, urinary diversion should be established with a suprapubic cystostomy**. Immediate management requires attention to two basic goals: Resuscitation of the patient and preparation for surgical replantation. The stump is covered with sterile saline-soaked gauze dressings. Transfusion may be required. The amputated penis is treated with a double-bag system. The amputated organ is wrapped in sterile saline gauze and placed in a bag, which is then placed into a second bag containing ice. Appropriate transfer to tertiary centers can be accomplished with **successful reimplantation after up to 16 hours of cold ischemia or 6 hours of warm ischemia.**

### Operative Management

Penile amputation requires precise management of urethral, cavernosal, neurovascular, and skin transection in all but the most distal injuries. Simple urethral and tunica albugineal reapproximation of complete shaft amputation will usually lead to survival and function of the organ, although skin loss is unavoidable and glans sensation and accompanying ejaculatory function will be lost. Urethral stricture is also common. Thus, **whenever possible, we advocate complete reattachment with microvascular and nerve reattachment**. With a clean cut, virtually no preparation is required. However, if the penis has been avulsed or cut with a blunt instrument or purposefully mutilated by the patient or the assailant, reattachment may be problematic.

Reapproximation proceeds ventrally to dorsally with the corpus spongiosum and urethral epithelium over a catheter, followed by the ventral-most aspect of the tunica albuginea of the corpus cavernosum. Reanastomosis of the deep arteries of the cavernosum is neither required nor easy (we perform dorsal artery reanastomosis only). Once the tunica albuginea of the corpus cavernosum has been reapproximated, the ends of the dorsal neurovascular structures are brought into proximity. Microvascular repair using an operating microscope and fine permanent suture allows reanastomosis of one or both dorsal arteries, the dorsal nerves, and the deep dorsal vein (Figure 10-12). Failure to reanastomose the deep dorsal vein may lead to glans hyperemia and venous congestion of the shaft skin, which can compromise the reattachment. Postoperative venous congestion is a major problem even with microvascular reattachment. The use of medical

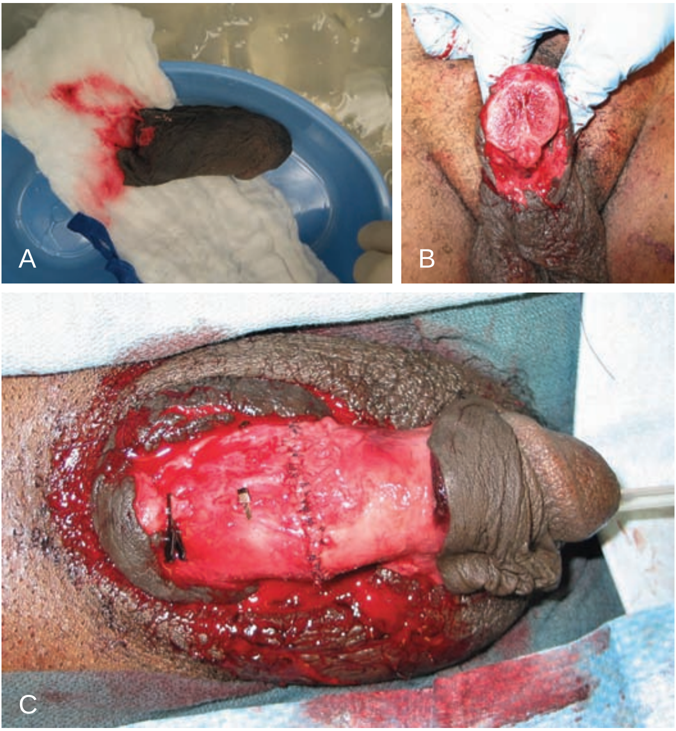


FIGURE 10-12A-C Penile amputation before and after repair. **A,** Detached distal phallus. **B,** Proximal penile stump. Note the transected corpora and urethra. **C,** Phallus after microscopic reanastomosis.

leeches is very helpful in reducing swelling and hematoma related to venous congestion and bleeding.

Normal sensation returns in over 80% of microscopic reimplantations but only 10% of macroscopic reconstructions. Erectile function normalizes in over 50% of patients repaired by either technique. If the distal penis is not available for reanastomosis, the corpora should be closed and a urethral neomeatus spatulated.

## GENITOURINARY SKIN INJURIES

### Scrotal Injuries

Lacerations and avulsions of the scrotum not involving the testis may occur due to blunt trauma, machinery accidents, stab wounds, and occasional firearm injury. Complete avulsion of the scrotal skin is rare and is usually the result of power takeoff, auger, or devastating motor vehicle crashes involving widespread skin loss or degloving.

#### *Operative Management*

Scrotal skin lacerations can be closed primarily in the absence of gross infection or heavy contamination. Deficits of up to 50% of the scrotal skin can often be closed primarily with good cosmetic results. Layered closure of the dartos fascia and skin, with a drain brought out dependently, limits postoperative hematoma. Xeroform gauze or other antibacterial dressings and ointments should be placed on the incisions, and the scrotum should be surrounded with loose gauze.

Complete scrotal avulsion is a devastating injury (Figure 10-13). The avulsed skin is not usually suitable for regrafting. We do not advocate immediate grafting but instead recommend an interval of local care, allowing the wound bed to granulate, after which very successful results can be obtained with split thickness skin grafts. Testicular transplantation into subcutaneous thigh pouches can be a temporizing or permanent measure dependent on patient age, sexual function, and overall prioritization of trauma injuries.

### Testicular Injuries

Small hematoceles (less than three times the size of the contralateral testicle) can generally be managed conservatively. Larger hematoceles should undergo operative evaluation because conservative

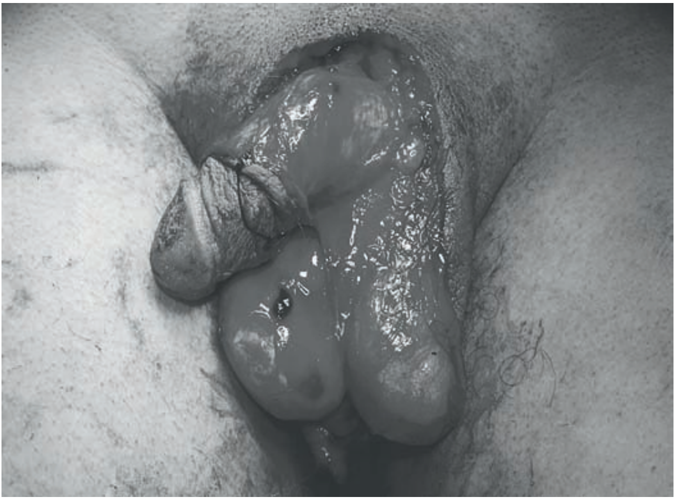


FIGURE 10-13 Scrotal and penile skin avulsion from machinery injury.

management often leads to higher rates of complications, longer recovery times, and increased need for delayed orchiectomy. The testes may also be dislocated outside of the scrotum, which should be considered in any nonpalpable testis in a trauma patient.

Testicular rupture generally presents as pain, nausea, and vomiting associated with an ecchymotic, tender, swollen hemiscrotum. This occurs in up to 50% of direct blunt scrotal traumas and should be considered in all blunt and penetrating scrotal injuries. **Scrotal ultrasound does not reliably differentiate traumatic testicular rupture from hematocele, and surgical exploration should be strongly considered in equivocal cases.** Testicular torsion should be considered in the differential diagnosis and can be evaluated with Doppler ultrasonography (Figures 10-14 and 10-15).

Penetrating trauma to the scrotum requires immediate surgical exploration.

### *Operative Management*

Large traumatic hematoceles should be drained surgically. **Testicular rupture should be managed with immediate exploration, debridement of devitalized seminiferous tubules, and,**

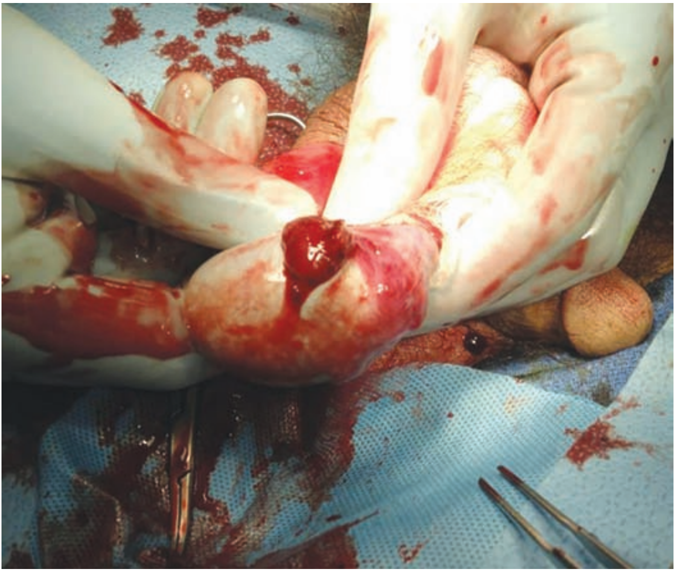


FIGURE 10-14 Intraoperative view of ruptured testis. Note the seminferous tubules protruding through the tunica albuginea.

**when possible, primary reapproximation of the tunica albuginea.** Use of a tunica vaginalis flap or graft can also be utilized for larger defects and/or to decrease intracompartmental pressure within the tunica albuginea. Early repair results in a high rate of testicular salvage and preserved endocrine function and fertility.

## Genital Bites

Bite injuries by animals or humans require appropriate antibiotic coverage for the species and tetanus toxoid administration when needed. Dog and cat bites most commonly lead to pathogenic infection with *Pasteurella* organisms; anaerobic organisms may also be present. The possibility of rabies transmission must be considered. Human bites are more likely to cause complications than dog bite wounds. Transmission of viral infection, including hepatitis and human immunodeficiency virus (HIV), is rare but possible.

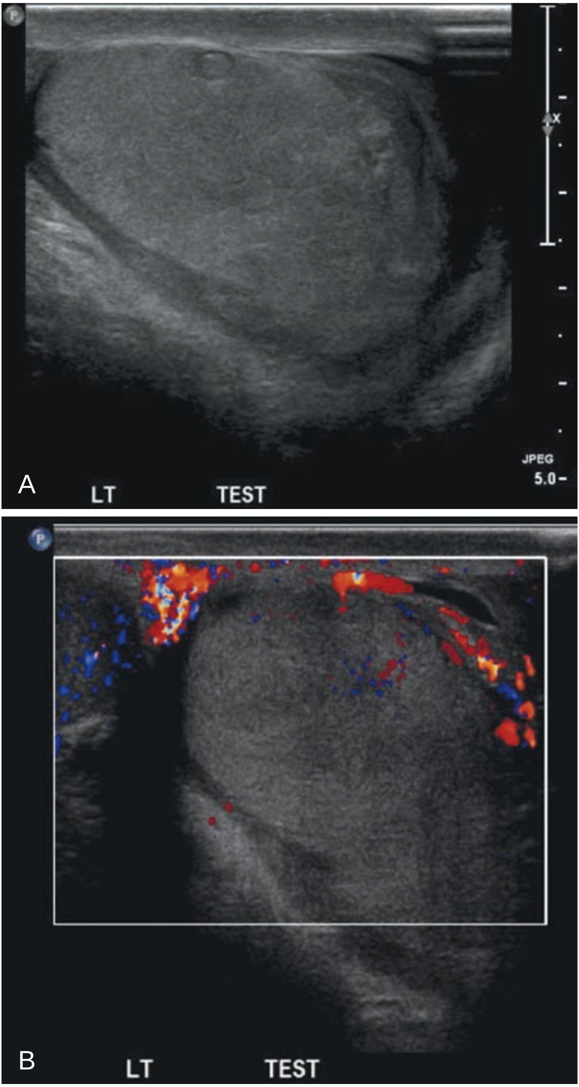


FIGURE 10-15 Ultrasound appearance of a left testicular rupture. *(A)* Sagittal view showing hemorrhage along the lateral aspect of the left testicle with disruption of the tunica albuginea and parenchymal heterogeneity inferiorly with a small associhematocele. *(B)* Transverse color flow view showing absent flow to the left testicle concerning for vascular compromise. (Courtesy of Dr. Parvati Ramchandani, University of Pennsylvania Health System)

### *Operative Management*

**Simple uncontaminated bite injuries can be irrigated and closed primarily if appropriate antibiotics are administered, contamination is minimal, and the wound is closed within 6 to 12 hours. Grossly contaminated bite injuries (including most human bites) should be left open and allowed to granulate.** Most penetrating injuries to the penis and genitalia can be closed primarily as long as devitalized tissue is conservatively debrided, foreign material is removed, and appropriate antimicrobial coverage is given. Xeroform gauze and loosely wrapped gauze sponges complete the dressing. Local application of antibiotic ointments should be started once the dressings are taken down.

## Genital Burns

Genital and perineal burns are present in less than 5% of burn victims. Because burns start superficially and progressively spread their damage down into deeper tissues in the opposite fashion from Fournier gangrene, preservation of some portion of the vascular integrity of the skin is likely in most chemical and thermal injuries. Due to the thinness of penile skin, burns to the penis are often full thickness.

Burns should be covered with appropriate dressings depending on the mechanism; 1% silver sulfadiazine cream is appropriate. Chemical burns can be irrigated with saline; alkaline burns with dilute acetic acid; and acid burns with sodium bicarbonate.

### *Operative Management*

**Management of burns, electrical injuries, and other skin injuries of the genitalia should be conservative.** The rich vascular supply may allow a greater degree of skin preservation than would be expected in other areas of the genitalia. When necessary, early resection of the eschar should be undertaken. Skin grafting for such injuries is a rare event. Complete loss of genital skin usually implies a devastating burn from which patients may be unlikely to survive. In contrast, less than complete surface area burns of the genitalia have a remarkable capacity for recovery, and split-thickness skin grafting is the exception rather than the rule.

# Injuries to the Female Genitalia

## MECHANISM

Female genital injuries involving severe pelvic fractures or sexual assault and interpersonal violence require specialized treatment. **Although many vulvar lacerations are the result of sports-related straddle-type injuries, genital trauma is reported in 20% to 53% of sexual assault victims. If such history is elicited, appropriate support services and police involvement must be secured.** Informed consent for the patient assessment should be obtained if a history of sexual assault has been verified. This assessment must include history, physical examination, and collection of laboratory and forensic specimens as outlined by the American College of Obstetrics and Gynecologists.

Female patients with external genital injuries should be suspected of having injury to the internal female organs, the lower urinary tract, and urethra. Many female urethral injuries are associated with vaginal bleeding. **Female genital injury in the setting of pelvic fracture or impalement injury should include cystourethrography, proctoscopy, and laparotomy as indicated.** Unrecognized associated urinary tract and gastrointestinal (GI) injuries in the face of vaginal trauma may lead to abscess formation, sepsis, and death.

## MANAGEMENT

Perineal and vulvar lacerations can usually be managed in the emergency department. Large hematomas should be incised and drained, with ligation of any bleeding vessels. As with the male genital skin, closure with interruptive absorbable sutures is standard. Drains can be used if there is a large cavity or suspected contamination or if hemostasis is suboptimal.

Internal lacerations to the vagina and cervix can be closed in the emergency department as long as there is not severe bleeding. Large lacerations associated with bleeding and hematomas require speculum examination under anesthesia to completely assess and repair the injuries. Vaginal lacerations are closed with continuous absorbable sutures, and vaginal packing is critical for hemostasis.

**Complex vaginal and perineal lacerations, associated with pelvic fracture, rectal injury, or other adverse features, require a more systematic approach.** Evaluation under anesthesia, including speculum examination, cystoscopy or cystography, and rigid proctoscopy, is mandatory. Diversion of the fecal stream is rarely indicated unless perineal injuries extensively involve the rectum, anus, or external sphincter. Bladder ruptures should be repaired if associated vaginal lacerations are present, to prevent deep pelvic infection, abscess, or formation of vesicovaginal fistulas.

## Conclusions

Urogenital trauma demands care and attention to prompt diagnosis, selection of management modality, integration of the multidisciplinary trauma team, and careful follow-up to monitor for long-term complications and disability.

### CLINICAL PEARLS

1. While most renal injuries can be managed nonoperatively, major hemorrhage still poses a risk of instability and even death. Clinical judgment remains paramount in these situations.
2. Ureteral injuries often present with nonspecific clinical signs and symptoms. They are frequently associated with significant nonurologic injuries. A high degree of suspicion is required to prevent delayed diagnosis and long-term morbidity.
3. For urethral injury associated with pelvic fracture, vigilance is required to detect associated bladder neck, rectal, and/or vaginal injuries that can lead to major complications and lifelong disability.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## Self-Assessment Questions

1. *What are the indications for imaging patients with suspected renal trauma? What imaging modalities are most helpful when managing these patients?*
2. *List the key principles of renal reconstructive surgery for trauma. Under what circumstances should a nephrectomy be performed?*
3. *How should one manage delayed bleeding after nonoperative management of major renal parenchymal laceration?*
4. *A patient who was involved in an automobile crash is found to have an extraperitoneal bladder rupture. What are the indications for operative management?*
5. *How should the urologist manage a traumatic posterior urethral injury?*
6. *A patient suffers a gunshot injury that transects the ureter just below the pelvic brim. What options would you consider for management?*
7. *A patient is transferred after a blunt scrotal trauma with a large left-sided hematocele. Scrotal ultrasound images show no obvious rupture of the testicle and good blood flow. How should you manage this patient?*

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## CHAPTER 11

# Urethral Stricture Disease

Michael J. Metro, MD

## Definition

1. **A urethral stricture results from fibrotic tissue that narrows the lumen and renders the normally compliant urethral lumen inelastic.** This results in the slowing or absence of urine flow through the area. Strictures occur as a result of inflammation or trauma from iatrogenic or external sources.
   a. The term *urethral stricture* is correctly used to describe lesions of the anterior urethra. In contrast, posterior urethral "strictures" are more accurately referred to as *pelvic fracture urethral distraction defects (PFUDD)* that occur in the setting of pelvic fracture. Other obstructive processes of the posterior urethra include prostatic stenosis or bladder neck contractures that occur as a result of prostatic radiation or surgery.
2. The anterior urethra begins at the urogenital diaphragm and includes the bulbar urethra, the penile or pendulous urethra, and the fossa navicularis and meatus.
3. The posterior urethra includes the prostatic and membranous urethra (Figure 11-1).

## Etiology

### TRAUMA

1. Anterior urethra
   a. Straddle injuries can injure the bulbar urethra when the urethra is crushed against the undersurface of the pubic symphysis.
   b. Penetrating injuries can involve the penile urethra.

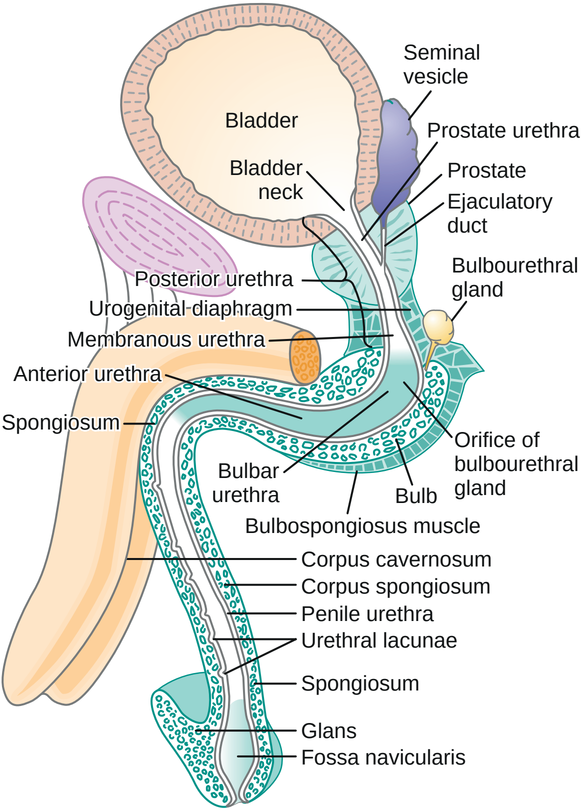


FIGURE 11-1 **Anatomy of anterior and posterior urethra.** (Courtesy of Jack W. McAninch, MD).

2. Posterior urethra
   a. **Urethral distraction defects as a result of pelvic fracture occur within the membranous urethra.** This roughly 2-cm-long segment is between two relatively fixed points (the prostatic apex and the proximal corpus spongiosum, which is fixed to the cavernous bodies).

### IATROGENIC

1. Injuries result from traumatic catheterization, instrumentation during other urologic surgeries (transurethral resection of the prostate [TURP], ureteroscopy), or self-induced injury from traumatic Foley catheter removal.

### INFECTION

1. Gonococcal urethritis classically causes anterior, mostly penile, urethra strictures, although these are less common in the antibiotic era.
2. Other sexually transmitted diseases such as *Chlamydia trachomatis* can also result in stricture disease.

### DIFFERENTIAL DIAGNOSIS

1. Bladder outlet obstruction from:
   a. Bladder neck contracture
   b. Prostatic obstruction
2. Meatal stenosis
3. Detrusor failure or atonic neurogenic bladder
4. Detrusor-sphincter dyssynergia

## Clinical Presentation

### OBSTRUCTION

1. The classic history is that of obstructive urinary symptoms, that is, slowing of urinary stream, decreased caliber of the stream, increase in voiding time, incomplete bladder emptying, and postvoid dribble.
2. Meatal strictures can result in splaying or splitting of the urinary stream.

### SECONDARY COMPLICATIONS

1. Infection
   a. Obstruction of the flow of urine often leads to “upstream” infections such as prostatitis or epididymoorchitis.

# Diagnosis

Diagnosis is largely clinical, based on history. Clinical suspicion can be supported by a flow rate and curve determination and/or assessment of postvoid residual. The shape of the flow curve is as important as or more important than the actual rate measurement. A "plateau" pattern, in which the flow rate reaches a rate and continues at this rate and no faster, is indicative of an obstructive process in the urethra.

## URETHROSCOPY

1. This can be used to confirm a clinical suspicion; accurate diagnosis of length and location of stricture should be performed radiographically.

## RETROGRADE URETHROGRAM (RUG) AND VOIDING CYSTOURTHROGRAM (VCUG)

1. **Accurate assessment of length and location of stricture is achieved by the correct performance of a RUG and a VCUG.**
2. The patient should be placed obliquely at 30 to 45 degrees, with the bottom leg flexed 90 degrees at the knee and the top leg straight. This allows unobstructed lateral imaging of the urethra and limits imaging foreshortening, which occurs with anteroposterior projection.
3. A 12- or 14-F Foley catheter is then placed within the fossa navicularis, and the balloon is inflated with 2 mL of saline to prevent dislodgment.
4. Contrast is then injected by the way of the catheter to opacify the urethra, and images are obtained.
5. In some cases, a voiding study is required to fully evaluate the stricture, especially in proximal lesions. The bladder is filled in a retrograde fashion via this catheter, or a small feeding tube (5 or 8 F) can be navigated through the stricture to allow for bladder filling. This component of the study can show what aspect of the urethral stricture is truly urodynamically significant as proximal dilation and distal diminution of urethral caliber will be seen (Figure 11-2).

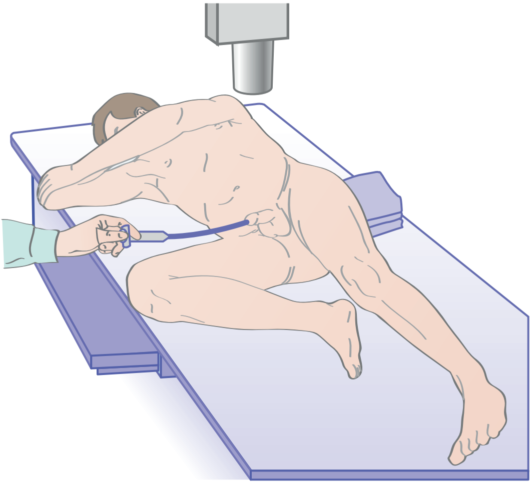


FIGURE 11-2 Positioning for performance of retrograde urethrogram (RUG). (Courtesy of Jack W. McAninch, MD).

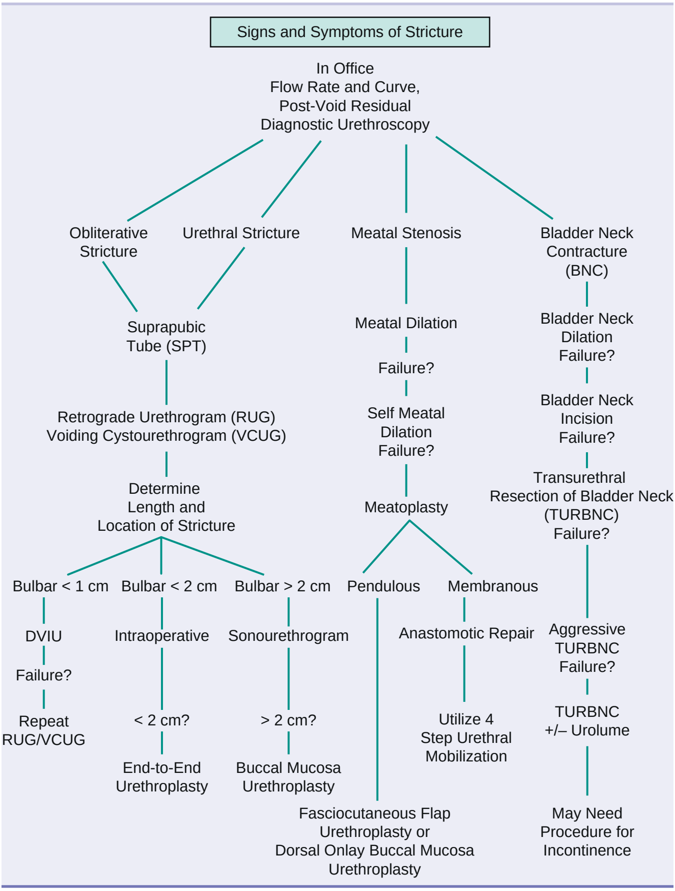
## Associated Conditions

1. Urethral carcinoma can present with a urethrocutaneous fistula secondary to urethral obstruction from stricture and must be ruled out with a biopsy in all patients presenting in this fashion.
2. Periurethral abscess proximal to distal obstruction from the urethral stricture
3. A urethral diverticulum can form proximal to the site of obstruction and cause postvoid dribbling or infections.

## Treatment

1. The first step in determining the course of treatment needs to involve a discussion of goals of therapy with the patient. Most treatments that involve dilation or incision can certainly treat the acute problems of urinary obstruction but do not have good long-term success rates (30% to 50%). Formal urethroplasty, utilizing a variety of techniques, can provide long-term success rates near 90% at the expense of a longer operation and longer immediate postoperative convalescence.

TABLE 11-1 **Algorithm for Diagnosis and Management of Urethral Strictures**



2. Algorithm for treatment (Table 11-1)
3. **Urethral dilation** can be performed in the office with local anesthesia with lidocaine jelly and is still a mainstay of therapy for stricture disease. A well-performed dilation may be the least traumatic of all of the minimally invasive techniques.

Urethral sounds or filiforms and followers can be employed to perform the dilation. Both techniques are not without risks, however. Urethral false passages and trauma can lead to development of longer and more complex strictures. Urethral dilation should be considered a palliative procedure as definitive successes are extremely rare.

4. A combination of flexible endoscopy and filiform placement can be a valuable tool to ensure correct luminal placement of the filiform. The filiform, placed in parallel next to the scope, is seen to transverse the stricture as opposed to a passage based on feel.
5. Soft dilation is a practice of the placement of a urethral catheter that is changed and increased in size over a period of days or weeks. This has not resulted in long-term success but can atraumatically extend the life of a dilation.
6. Direct vision incisional urethrotomy (DVIU)
    a. Incisional urethrotomy is performed endoscopically under sedation or general anesthesia and involves visualizing the stricture endoscopically and incising with a cold knife at the 12 o'clock position to open the stricture. A Foley catheter is then placed for 2 to 10 days. The goal of the incision is to allow for reepithelialization of the urethral lumen, which will result in a lumen of normal caliber.
    b. A variation of the aggressive DVIU incision at the 12 o'clock position is multiple small, shallow incisions in a stellate pattern—the *radial DVIU*. Theoretically, this causes less damage and may result in a recurrence that is only minimally longer and more complex than the original stricture, making formal open urethroplasty easier to perform.
    c. Urethrotomies with a hot knife or a laser should be avoided, secondary to the addition of thermal injury to the spongiosal tissue making recurrences longer and more severe.
    d. Results
        1) The success rate of incisional urethrotomy depends on length and location of the stricture. Short-term (less than 6 months) success rates are excellent, but long-term success occurs in only 50% of cases. Subsequent urethrotomies have an even lower chance of long-term success with the second having a 20% chance of success and the

    third having virtually no chance of success. Incisions of pendulous strictures should be considered palliative as true long-term successes are rare.
  2) A regimen of urethral self-dilation after DVIU or dilation can extend the life of a urethrotomy and lengthen the time needed for subsequent incisions or dilations. This has not proven to provide any higher long-term success rates, however.
  3) Injections of steroids into strictures after incisions have been studied but have not resulted in improved outcomes.

e. Conclusions
  1) Despite low long-term success rates, dilations and incisions of a urethral stricture are commonly repeatedly performed. Referral to a urologist with specific training in urethral reconstruction does not happen as often as it probably should. The open reconstructive procedures are technically difficult and are not a casual operation. Repeated incisions and dilations should be considered palliative and not therapeutic unless the only aim is to establish urethral continuity. Management guidelines generally recommend referral for urethroplasty in young individuals and those that have had one or two failed endoscopic attempts at treatment, depending on the stricture characteristics.

## Open Reconstruction

1. The optimal choice of techniques for formal open reconstruction of a urethral stricture is dependent on length and location of stricture as determined by retrograde urethrography.
2. Intraoperative sonourethrography can provide data at the time of surgery, including exact length of stricture, degree of luminal narrowing, and location that may help in determining technique for reconstruction.
3. The sonourethrogram is performed by placing a 10- or 12-MHz small parts transducer in the perineum with the patient placed in a frog-leg position. Saline is injected via a catheter-tipped syringe to distend the urethra in a retrograde fashion. The bladder is filled and suprapubic pressure is applied to

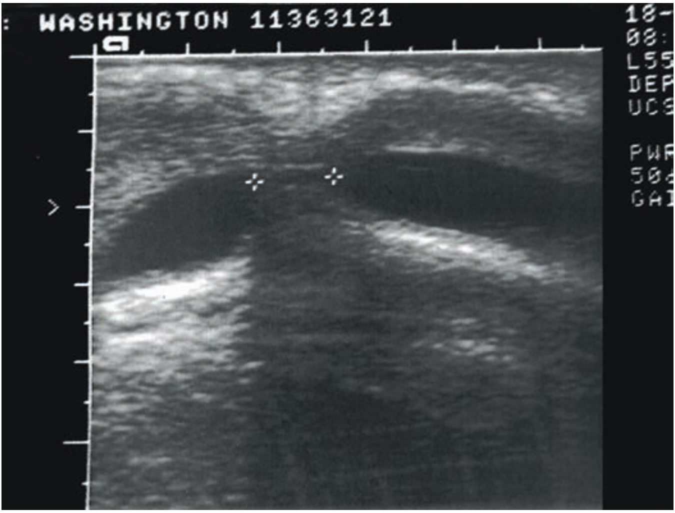


FIGURE 11-3 **Sonourethrogram.** (Courtesy of Jack W. McAninch, MD).

provide antegrade filling of the urethra. The stricture can then be measured and the degree of luminal narrowing can be determined, which aids in determining the width of a flap or graft that may be required (Figure 11-3).

## ANASTOMOTIC URETHROPLASTY

1. Indications
   a. Bulbar strictures less than 2 cm can reliably be treated with an anastomotic or end-to-end (ETE) urethroplasty.
   b. Penile or pendulous strictures, unless exceedingly short or in an impotent man, cannot be managed by ETE because of the resultant chordee that will be present postoperatively. The pendulous urethra lacks the elasticity of the bulbar urethra, and its location on the penile shaft makes chordee with an erection unavoidable.
2. Procedure
   a. The urethra is mobilized by dividing the fibromuscular septum, which attaches the urethra dorsally to the cavernosal bodies. Mobilization is performed until a tension-free anastomosis is

performed over a 16-F urethral catheter. The anastomosis is performed in one layer dorsally where the spongiosum is thin and in two layers ventrally where the spongiosum is robust.

   b. Urethroscopy and cystoscopy should be performed after the urethra is opened to document absence of more proximal stricture or foreign bodies (stones) in the bladder.

3. Postoperative
   a. The urethral catheter is maintained for 2 weeks.
   b. A VCUG is done at the time of catheter removal to document the absence of extravasation and the presence of an adequate caliber urethra. The bladder is filled via the existing urethral catheter and is then removed. Fluoroscopic visualization of the subsequent void is performed.
4. Success rate
   a. Long-term success rates between 90% and 95% should be expected.
   b. Success is defined by the presence of a normal flow rate, an unobstructed flow pattern, and the absence of the need for subsequent instrumentation such as dilation or incision.
   c. Self-dilation or calibration after all open urethroplasty cases is not required and should be discouraged.

## SUBSTITUTION URETHROPLASTY

1. Substitution urethroplasty is performed for bulbar strictures greater than 2 cm and for most pendulous strictures. Grafts rely on the blood supply of surrounding tissues for support, whereas flaps bring their own pedicled blood supply for use in areas where blood supply is less robust or reliable.
2. The penile urethra circular fasciocutaneous flap, described by Jack McAninch, has been a mainstay of reconstruction for strictures for the entire anterior urethra. More recently, with the popularity of the buccal mucosa graft, its use is reserved for pendulous strictures or for reoperations in the bulbar urethra where a free graft repair has failed.
3. The flap is raised by marking two parallel circumferential incisions, usually 1.5-2.0 cm apart, under the coronal margin. The proximal incision is taken down above the superficial lamina of Buck fascia and carried toward the base of the penis. The

distal incision is carried below this layer of Buck fascia and again taken down to the base of the penis. In this fashion, a pedicled flap, usually 15-18 cm in length, and dependent on the superficial lamina of Buck fascia for vascular support, can be raised.

4. The flap is utilized as a ventral onlay after the urethra has been opened ventrally through the stricture. 6-0 Maxon or PDS is used to perform a running anastomosis that incorporates the flap and the dorsal urethral plate over a 16-F catheter.
5. The catheter is left for 3 weeks at which time a VCUG confirms adequate healing.
6. Long-term success rates are between 85% and 90%.
7. **Buccal mucosa:** For substitution urethroplasty in the bulbar urethra, the buccal mucosa graft has achieved huge popularity and should be considered the gold standard.
   a. **Properties:** Buccal mucosa has a thick epithelium that makes it easy to handle, has a thin lamina propria that improves graft take, and is an epithelial surface that is accustomed to being wet, leading to less inflammation.
   b. **Harvest:** Grafts can be harvested from the inner cheek, the lower lip, and even the lateral tongue (a lingual graft).
   c. **Dorsal or ventral** grafts can be placed as dorsal or ventral onlays, depending on surgeon preference. Advocates of the ventral approach point to the improved vascularity of the corpus spongiosum over the corporal bodies, which support the dorsal onlay graft, and the relative simplicity of the surgical technique. Those that favor the dorsal onlay (see Table 11-1) point to a lesser incidence of graft sacculation due to improved mechanical support of the corporal bodies and the ability to place that graft in less vascularly robust areas of the urethra such as the pendulous urethra (Figures 11-4 and 11-5).
   d. **ASOPA:** An interesting technique that has made a dorsal onlay technique easier is the dorsal inlay procedure described by Hari S. Asopa. In this technique, an initial ventral urethrotomy is made at the site of the stricture. This is followed by a dorsal urethrotomy, which is then mobilized laterally off of the corporal bodies. The graft is then placed as an inlay, and then the ventral urethrotomy is closed in two layers. This avoids

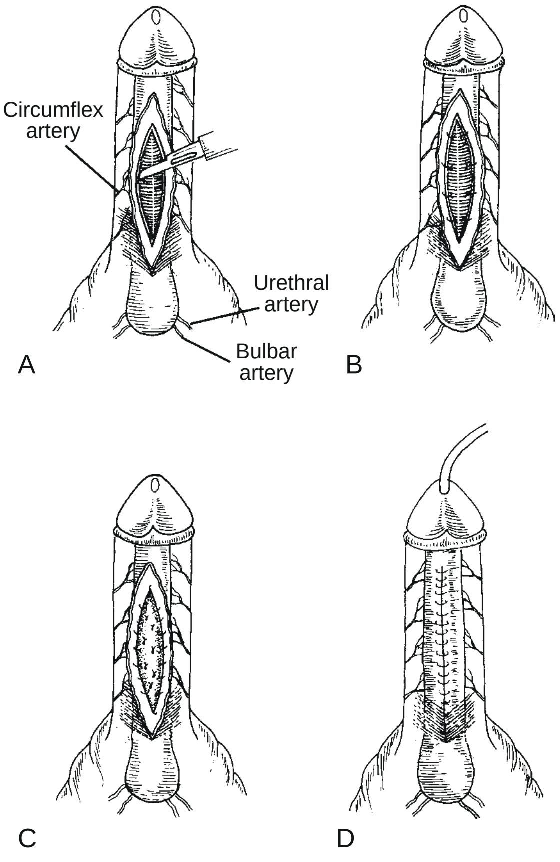


FIGURE 11-4 **A,** Separation of margins of dorsal urethrotomy from corporal bodies. **B,** Securing of free margins to tunica albuginea. **C,** Fixation of dorsal free graft. **D,** Retubularization of urethra. (From Asopa HS, Garg M, Singhal GG, et al: Dorsal free graft urethroplasty for urethral stricture by ventral sagittal urethrotomy approach, *Urology* 58, 2001.)

the complete mobilization of the urethra that is required in the dorsal onlay technique, which is more technically challenging. Opponents of this technique point to the additional urethrotomy required to complete the procedure that potentially leads to a higher incidence of fistula and ischemia.

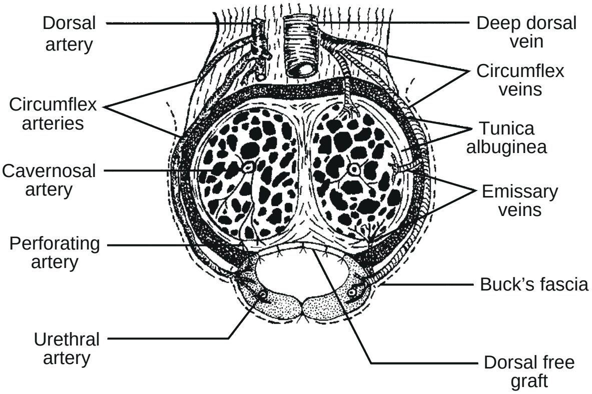


**FIGURE 11-5 Cross-section of penis showing arterial supply of urethra on right and venous drainage on left, along with dorsal free graft and retubularized urethra.** (From Asopa HS, Garg M, Singhal GG, et al: Dorsal free graft urethroplasty for urethral stricture by ventral sagittal urethrotomy approach, *Urology* 58, 2001.)

## Posterior Urethra

Pelvic fracture urethral distraction defects (PFUDDs): Strictures of the posterior urethra are more properly referred to as PFUDDs. The membranous urethra is short (2 cm) and is positioned between two relatively fixed points (prostatic apex and the proximal corpus spongiosum). Ten percent of all pelvic fractures result in posterior urethral disruptions that occur due to the shearing forces applied at the membranous urethra. Urethral disruptions are more common with anterior disruptions of pelvic ring and with bilateral rami fractures.

### DIAGNOSIS

The classic presentation of the posterior urethral disruption is blood at the urethral meatus, which occurs in up to 93% of cases. The diagnosis is also made when attempts at urethral catheter placement fail. A rectal exam may reveal a high-riding prostate, which is present due to the prostate being elevated out of the pelvis secondary to surrounding hematoma. Diagnosis is confirmed by RUG, which may reveal a complete or partial disruption or a contusion in which the lumen is compressed by surrounding hematoma but remains in continuity. A complete disruption is present when no injected contrast is found to enter the bladder but some contrast is able to enter the bladder when a partial disruption is present.

## INITIAL MANAGEMENT

Some controversy exists in the initial management of a posterior urethral disruption. Some experts advocate only urinary diversion with a suprapubic catheter placement, whereas some recommend an attempt at urethral realignment when the clinical situation allows. Advocates for realignment point to a decreased stricture rate of 70% versus nearly 100% with simple diversion. Proponents of suprapubic diversion point to a minor increase in the incidence of impotence and incontinence with realignment. It also appears that if an initial realignment procure is chosen, the surgeon is more prone to continue repeated endoscopic management of recurrences that are doomed to failure.

1. Anastomotic: All repairs of PFUDDs are anastomotic or ETE repairs. The goal of the surgery is to mobilize the urethra enough to ensure an anastomosis that is tension free. A stepwise approach to this urethral mobilization has been outlined by George Webster and others. The four-step approach entails:
    a. **Division of dorsal attachments of the urethra to the corpus cavernosum:** This can be carried distally to the penoscrotal junction with no risk of chordee.
    b. **Crural separation:** Separation of the corporal bodies for 3-4 cm forms a groove in which the urethra can lie within to allow for a more direct route to the proximal urethra.
    c. **Inferior pubectomy:** Removal of a portion of the inferior pubis with a rongeur or osteotome also allows for a more direct route for the distal urethra to travel to reach the proximal urethrostomy.
    d. **Urethral rerouting:** Finally, urethral rerouting around a corporal body allows the urethra to lie in a more dorsal fashion, thus shortening the distance between the two urethral ends.

## RESULTS

Success rates of 90% or more should be expected when performed by surgeons familiar with the technique. It is important to note that some degree of erectile dysfunction (ED) occurs in up to 70% of men with posterior urethral injuries. A recovery of function is the rule in more than 60% of these patients after definitive urethroplasty and resolution of the pelvic hematoma. Incontinence is rare with only 6% of men reporting problems with stress incontinence.

## Bladder Neck Contractures

Bladder neck or vesical neck contractures occur as a result of prostatic surgery and can be very difficult to treat because the recurrence rate is high. An incidence of 5% to 15% can be expected after radical retropubic prostatectomy and approximately 3% after TURP. Initial treatment usually is a bladder neck dilation, followed by incisions, and then finally resections of the vesical neck.

Most reconstructive surgeons favor cold radial incisions into a bladder neck contracture in an effort to avoid adding a thermal injury to the trauma of the incision. This may lead to more scar tissue formation. This theory is also why laser incisions are generally avoided.

There has been recent data to suggest that the injection of mitomycin C after incision may add to the success rate of a simple cold incision.

The result of "fixing" a bladder neck contracture can be stress incontinence and patients must be made aware of this. Formal open reconstruction of the bladder neck often requires an abdominoperineal approach and can be quite difficult. Continence is rare after such a procedure. The one remaining acceptable place for a UroLume stent may be across the bladder neck in refractory cases of contracture. An artificial urinary sphincter is sometimes necessary to regain continence once a contracture is definitely treated.

## Specific Conditions Causing Urethral Stricture

1. Balanitis xerotica obliterans (BXO) is the term used to describe genital lichen sclerosis in the male. Histologically, it is characterized by hyperkeratosis and lymphocytic infiltration.
   a. Patients with BXO present most commonly with meatal stenosis and have findings of loss of elasticity of the glanular and preputial skin, loss of skin pigment, and induration and hyperkeratosis of the glans.

   b. Conservative treatment involves application of topical steroids (betamethasone, clobetasol) and meatal dilation.
   c. Assessment must include retrograde urethrography because the disease can involve the more proximal urethra, or prior instrumentation may have induced stricture disease here.
   d. Formal reconstruction often involves substitution urethroplasty with buccal mucosa, often in two stages, as the penile skin, often used to treat strictures here, is often histologically abnormal in these patients and repairs based on flap of this tissue are bound to fail.

2. Fossa navicularis strictures are almost always caused by iatrogenic trauma from instrumentation when not caused by BXO.
   a. Local flap urethroplasty is the mainstay of definitive treatment for strictures in this area. The ASOPA technique of a dorsal inlay buccal mucosa urethroplasty is valuable here also.

3. The *hypospadias cripple* is a term used to describe the unfortunate man who has undergone prior failed hypospadias repair, usually multiple times. Strictures in these men are usually complex and require expert referral for formal reconstruction, which usually involves two-stage reconstruction with buccal mucosa grafting.

## CLINICAL PEARLS

1. The anterior urethra begins at the urogenital diaphragm and includes the bulbar urethra, the penile or pendulous urethra, and the fossa navicularis and meatus.
2. The classic history is that of obstructive urinary symptoms, that is, slowing of urinary stream, decreased caliber of the stream, increase in voiding time, incomplete bladder emptying, and post-void dribble.
3. A urethral stricture is largely a clinical diagnosis based on history. Clinical suspicion can be supported by a flow rate and curve determination and/or assessment of post-void residual or by performing a urethroscopy. Diagnosis should be confirmed with the performance of a retrograde urethrogram and/or voiding cystourethrography.
4. The first step in determining course of treatment needs to involve a discussion of goals of therapy with the patient. Most treatments that involve dilation or incision can certainly treat the acute problems of urinary obstruction but do not have good long-term success rates (30%-50%). Formal urethroplasty, utilizing a variety of techniques, can provide long-term success rates near 90% at the expense of a longer operation and longer immediate postoperative convalescence.

5. Strictures of the posterior urethra are more properly referred to as PFUDDs (Pelvic Fracture Urethral Distraction Defects). The membranous urethra is short (2 cm) and is positioned between two relatively fixed points (prostatic apex and the proximal corpus cavernosum via the dorsal fibromuscular septum).
6. *Balanitis xerotica obliterans (BXO)* is the term used to describe genital lichen sclerosis in the male and female. Histologically it is characterized by hyperkeratosis and lymphocytic infiltration.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What is the anatomic landmark that separates the anterior from the posterior urethra?*
2. *What are the main causes of stricture disease?*
3. *What are the symptoms of stricture disease?*
4. *What are the noninvasive and invasive diagnostic tests used to diagnose urethral strictures?*
5. *What is the correct technique and patient positioning to perform a retrograde urethrogram (RUG)?*

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## CHAPTER 12

# Urinary Fistula

Ariana L. Smith, MD • Eric S. Rovner, MD

The World Health Organization estimates that there are 130,000 new cases of urogenital fistula per year worldwide. This number likely underestimates the true incidence because many patients in developing countries lack access to care. **A fistula represents an extra-anatomic communication between two or more epithelial or mesothelial lined body cavities or the skin surface.** Although most fistulas in the industrialized world are iatrogenic, they may also occur as a result of parturition (the most common etiology worldwide), congenital anomalies, malignancy, inflammation and infection, radiation therapy, surgical or external tissue trauma, foreign bodies, ischemia, and a variety of other processes. The potential exists for fistula formation between a portion of the urinary tract (i.e., kidney, ureters, bladder, urethra) and virtually any other body cavity, including the reproductive organs, gastrointestinal (GI) tract, chest (pleural cavity), lymphatics, vascular system, genitalia, and skin. The presenting signs and symptoms are variable and depend to a large degree on the involved organs, the presence of underlying urinary obstruction or infection, the size of the fistula, and associated medical conditions such as malignancy.

Treatment of urinary fistula depends on several factors, including its location, size, etiology (malignant or benign), and surrounding tissue quality.

## Vesicovaginal Fistula

### GENERAL CONSIDERATIONS

Vesicovaginal fistula (VVF) is the most common acquired fistula of the urinary tract.

## ETIOLOGY

The most common cause of VVF differs in various parts of the world.

1. In the industrialized world, the most common cause is injury to the bladder at the time of gynecologic surgery—usually hysterectomy for benign conditions (60% to 75%), followed by hysterectomy for malignant conditions (30%), caesarean section (6%), and obstetric injuries (1%).
   a. Posthysterectomy VVFs are thought to result most commonly from an unrecognized cystotomy near the vaginal cuff.
      1) The operative approach to hysterectomy is an important factor because bladder injuries are at least three times more common during laparoscopic or abdominal hysterectomy compared to vaginal hysterectomy.
   b. **The incidence of fistula after hysterectomy is estimated to be approximately 0.1% to 0.2%.** The injury rate to the urinary tract is much higher than this because most injuries do not result in fistula. Patients who develop a VVF are more likely to have a large cystotomy, greater tobacco use, larger uterine size, and more operative blood loss.
   c. Other causes of VVF in the industrialized world include malignancy, pelvic radiation, and obstetrical trauma, including forceps lacerations and uterine rupture.

2. In the developing world where routine obstetrical care may be limited, VVFs most commonly occur as a result of prolonged obstructed labor with resulting pressure necrosis and tissue ischemia to the pelvic floor. The anterior vaginal wall, trigone, and urethra generally experience the greatest direct pressure from the trapped fetus. In some instances, VVF may result from the use of forceps or other instrumentation during operative delivery.
   a. Obstetric fistulas tend to be larger, located distally in the vagina, and may involve the proximal urethra.
   b. The constellation of problems resulting from obstructed labor is not limited to VVF and has been termed the *obstructed labor injury complex* and includes varying degrees of each of the following: Urethral loss, stress incontinence,

hydroureteronephrosis, renal failure, rectovaginal fistula, rectal atresia, anal sphincter incompetence, cervical destruction, amenorrhea, pelvic inflammatory disease (PID), secondary infertility, vaginal stenosis, osteitis pubis, and foot drop.

   c. In sub-Saharan Africa the incidence rate of obstetric VVF has been estimated at 10.3 per 100,000 deliveries.

## PRESENTATION

1. The most common complaint is constant urinary drainage per vagina, although small fistulas may present with intermittent wetness that is positional in nature and mistaken for stress incontinence.
   a. VVF must be distinguished from urinary incontinence resulting from other causes such as stress (urethral) incontinence, urgency (bladder) incontinence, and overflow incontinence.
   b. Patients may also complain of recurrent cystitis, perineal skin irritation caused by constant wetness, vaginal fungal infections, or rarely pelvic pain. When a large VVF is present, patients may not void at all and simply have continuous leakage of urine into the vagina.
   c. VVF following hysterectomy or other surgical procedures may present on removal of the urethral catheter or may present 1 to 3 weeks later with urinary drainage per vagina.
      1) VVFs resulting from hysterectomy are usually located high in the vagina at or just anterior to the vaginal cuff (Figure 12-1).
   d. VVF resulting from radiation therapy may not present for months to years following completion of radiation. These tend to represent some of the most challenging reconstructive cases in urology because of the size, complexity, and the associated voiding dysfunction caused by radiation effects on the bladder. The tissue ischemia that results from radiation therapy may involve the surrounding tissues, limiting reconstructive options.

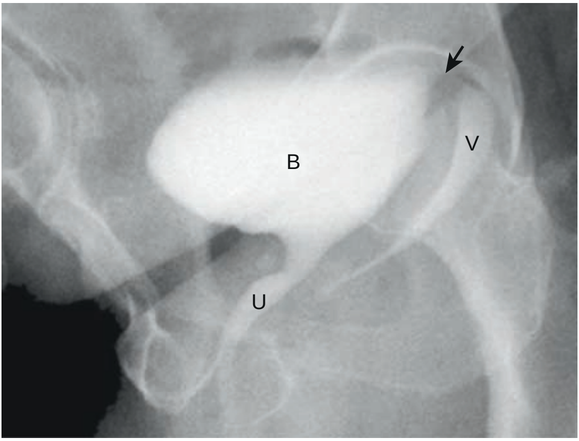

FIGURE 12-1 Voiding cystourethrogram (VCUG) demonstrating a VVF high at the level of the vaginal cuff in a patient following hysterectomy. The arrow demonstrates the fistula tract (not well seen). **B,** urinary bladder; **U,** urethra; **V,** vagina.

## EVALUATION (FIGURE 12-2)

1. History
2. Physical examination
   a. A pelvic exam with speculum should always be performed in an attempt to locate the fistula and assess the size and number of fistulas.
   b. Palpate for masses or other pelvic pathology, which may need to be addressed at the time of fistula repair.
   c. An assessment of inflammation surrounding the fistula is necessary because it may affect timing of the repair.
   d. **The presence of a VVF** may be confirmed by instilling vital blue dye or sterile milk into the bladder per urethra and observing for discolored vaginal drainage.
      1) A **double dye test** may confirm the diagnosis of urinary fistula and suggest the possibility of an associated ureterovaginal or urethrovaginal fistula. A tampon is placed per vagina. Oral phenazopyridine is administered and vital blue dye is instilled into the bladder. If the tampon is discolored yellow-orange at the top, a ureterovaginal fistula is suggested. Blue discoloration in the midportion

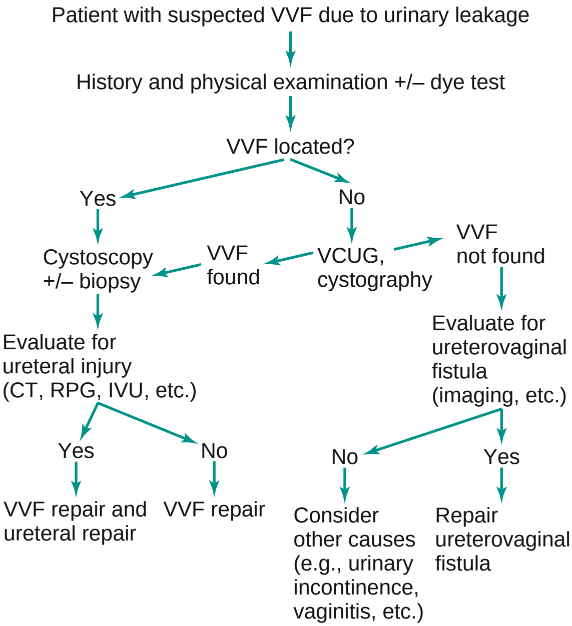
Patient with suspected VVF due to urinary leakage
History and physical examination +/– dye test
VVF located?
Yes
No
Cystoscopy +/– biopsy
VVF found
VCUG, cystography
VVF not found
Evaluate for ureteral injury (CT, RPG, IVU, etc.)
Evaluate for ureterovaginal fistula (imaging, etc.)
Yes
No
No
Yes
VVF repair and ureteral repair
VVF repair
Consider other causes (e.g., urinary incontinence, vaginitis, etc.)
Repair ureterovaginal fistula

FIGURE 12-2 Algorithm for diagnosis of vesicovaginal fistula (VVF).

of the tampon suggests VVF, whereas blue staining at the bottom suggests a urethrovaginal fistula.

3. Urine culture and urine analysis
4. Cystoscopy and possible biopsy of the fistula tract are performed if malignancy is suspected.
   a. Note the location of fistula relative to ureters; repair of the fistula may require reimplantation of ureters if the fistula involves the ureteral orifice.
   b. The presence of foreign bodies, including suture material, mesh, and/or bladder calculi, should be assessed.
5. Voiding cystourethrography
   a. Some small fistulas may not be seen radiographically unless the bladder is filled to capacity and a detrusor contraction is provoked.
      1) Assesses for vesicoureteral reflux.

        2) Examines for multiple fistulas including urethrovaginal fistula.
        3) Assesses size and location of fistula.
6. Intravenous urography (IVU), computed tomography urography (CTU), and/or retrograde pyeloureterography
    a. Assesses for concomitant ureteral injury and/or ureterovaginal fistula, which has been reported to occur in up to 12% of patients.
    b. Contrast material in the vagina, air in the bladder, and bladder wall thickening are signs suggestive of the presence of a fistula.
7. Cross-sectional pelvic imaging (magnetic resonance imaging [MRI]/computed tomography [CT]) if malignancy is suspected.

## DIFFERENTIAL DIAGNOSIS

***Differential diagnosis of a vesicovaginal fistula (VVF) includes:***

Stress incontinence
Urgency incontinence
Overflow incontinence
Complete gravitational incontinence
Ureterovaginal fistula
Urethrovaginal fistula
Vesicouterine fistula
Peritoneal fluid leak

## THERAPY

1. Nonsurgical management
    a. **Catheter drainage** is the initial treatment in most cases when the VVF is recognized early in the clinical course and an epithelialized tract has not yet had an opportunity to form. Antibiotics, anticholinergics, and topical estrogen creams are adjuvant measures to prevent infection, promote bladder relaxation, and facilitate healing.
    b. **Fulguration of the fistula tract** with electrocautery followed by catheter drainage has been shown to have some efficacy in small (less than 5 mm), uncomplicated fistulas.
    c. Adjuvant measures such as **fibrin glue** have been reported in small patient series in conjunction with fulguration and catheter drainage as a “plug” in the fistula and as “scaffolding” to allow the ingrowth of healthy tissue.

TABLE 12-1 **Principles of Vesicovaginal Fistula Repair**

1. Adequate exposure of the fistula tract with debridement of devitalized and ischemic tissue
2. Removal of involved foreign bodies or synthetic materials from region of fistula if applicable
3. Careful dissection and/or anatomic separation of the involved organ cavities
4. Watertight closure
5. Use of well-vascularized, healthy tissue flaps for repair (atraumatic handling of tissue)
6. Multiple layer closure
7. Tension-free, nonoverlapping suture lines
8. Adequate urinary tract drainage and/or stenting after repair
9. Treatment and prevention of infection (appropriate use of antimicrobials)
10. Maintenance of hemostasis

2. Surgical management
    a. Success rates approach 90% to 98% regardless of surgical approach.
    b. Adherence to basic surgical principles is essential to achieve successful repair of all urinary fistulas (Table 12-1).
    c. **The timing of the repair** should take into consideration the degree of inflammation, presence of infection, general health and nutritional status of the patient, and patient comfort. **Early intervention is advocated for the vast majority of situations in the developed world. In the setting of significant inflammation, infection, or radiation damage, a 3- to 6-month waiting period is advised.**
    d. Choice of the optimal surgical approach to VVF is controversial, and there are numerous factors to consider (Table 12-2). No single approach is applicable to all VVFs.
        1) **Transabdominal approach:** The bladder is exposed and opened in the sagittal plane down to the level of the fistula through a midline infraumbilical incision, a Pfannenstiel incision, or a laparoscopic or robotic approach. The bladder is separated off the vagina beyond the level of the fistula. The fistulous tract is biopsied if there is any concern for malignancy and debrided back to healthy tissue if necrotic. The bladder and vagina are closed separately, in multiple layers, with incorporation of the fistula tract in most situations. Often, well-vascularized tissue such as

TABLE 12-2 **Abdominal Versus Transvaginal Repair of Vesicovaginal Fistula**

| | **Abdominal** | **Transvaginal** |
|---|---|---|
| Length of hospitalization | 4-7 days | 1-2 days |
| Timing of repair | Usually delayed 2-6 months from the time of initial injury | May be done immediately in the absence of infection |
| Location of ureters relative to fistula tract | Fistula located near ureteral orifice may necessitate reimplantation | Reimplantation may not be necessary even if fistula tract is located near ureteral orifice |
| Sexual function | No change in vaginal depth | Potential risk of vaginal shortening or stenosis |
| Location of fistula tract/ depth of vagina | Fistula located low on the trigone or near the bladder neck may be difficult to expose | Fistula located high at the vaginal cuff may be difficult to expose |
| Use of adjunctive flaps | Omentum, peritoneal flap, intestine | Labial fat pad (Martius fat pad), peritoneal flap, gracilis muscle, labial myocutaneous flap |
| Relative indications | Large fistulas, located high in a deep vagina, radiation fistulas, failed transvaginal approach,<br>small capacity bladder requiring augmentation,<br>need for ureteral reimplantation,<br>inability to place patient in the lithotomy position | Uncomplicated fistulas, low fistulas<br>Vaginal exposure may be difficult in some nulliparous patients |

omentum is interposed between the vagina and bladder as an additional layer to promote healing and prevent recurrence. When omentum cannot be mobilized, peritoneum is used as an interposition layer.

2) **Transvaginal approach:** Many vaginal approaches have been described, including Sims, Latzko, and Raz. Generally, an inverted U incision is made and the vaginal wall mobilized circumferentially around the fistula tract. Either the fistula tract is excised with edges of the debrided tract forming the first layer of closure, or the tract is left in situ with fistula edges rolled over, forming the primary layer of closure. The perivesical fascia on either side of the first layer of closure is then imbricated over the primary suture line forming the second layer. A labial fat pad (i.e., Martius flap), peritoneal flap, or gracilis muscle flap may be placed over the suture lines as a well-vascularized flap similar to the omental flap in the transabdominal approach. Finally, a flap of vaginal wall is advanced over the repair, forming the final layer of closure. The Latzko technique involves denuding the vaginal epithelium around the fistula tract and performing a partial colpocleisis. While this technique can shorten the vagina and may not be desirable in sexually active women, it can concomitantly treat pelvic organ prolapse in sexually inactive women opting for minimally invasive surgery.

e. Regardless of approach, maximal urinary drainage (with urethral and/or suprapubic catheter) is maintained postoperatively. A cystogram is usually obtained 2 to 3 weeks following repair to confirm successful closure. Antimuscarinic or beta-3 agonist medications may be prescribed to help promote bladder relaxation and assist the patient in tolerating the catheter(s).

## Ureterovaginal Fistula

### ETIOLOGY

Most ureterovaginal fistulas are secondary to unrecognized distal ureteral injuries sustained during **gynecologic procedures,** including laparoscopic, abdominal or vaginal hysterectomy, caesarean section, prolapse surgery, and anti-incontinence surgery. Occasionally, they may be secondary to endoscopic instrumentation, radiation therapy, pelvic malignancy, penetrating pelvic trauma, or other pelvic surgery (vascular, enteric, etc.).

1. Risk factors for ureteral injuries include a prior history of pelvic surgery, endometriosis, radiation therapy, and PID.
2. Up to 12% of VVFs may have an associated ureterovaginal fistula.

## PRESENTATION

Ureterovaginal fistulas may present with clear drainage per vagina or unilateral hydroureteronephrosis and flank pain secondary to partial ureteral obstruction.

Flank pain, nausea, fever, and clear vaginal drainage following pelvic surgery are very suggestive of ureteral injury. Patients will have a normal voiding pattern if the contralateral kidney is unaffected.

## EVALUATION

1. IVU or CT urography: A urogram may demonstrate partial obstruction, hydroureteronephrosis, and drainage into the vagina.
2. Cystoscopy and retrograde pyelography can be performed to evaluate for bladder injury and to visualize the distal ureteral segment if not well seen on the urogram. **An attempt at retrograde stenting is reasonable if the pyeloureterogram demonstrates ureteral continuity.** Prolonged internal diversion (6 to 8 weeks) with ureteral stenting may result in resolution of the fistula.
3. CT/MRI: Cross-sectional imaging may be useful to evaluate for pelvic malignancy when indicated or to evaluate for a urinoma in patients with persistent fevers.
4. Cystogram or cystometrogram: In cases in which a long segment of distal ureter is involved and a Boari flap is being considered for reconstruction, a cystogram or cystometrogram may be useful to evaluate the bladder capacity. In addition, a cystogram should evaluate for vesicoureteral reflux.
5. Percutaneous nephrostomy and antegrade nephrostogram: Percutaneous drainage of the involved kidney followed by antegrade instillation of contrast can provide decompression of a partially obstructed kidney, and anatomic localization and demonstration of the fistula (Figure 12-3).

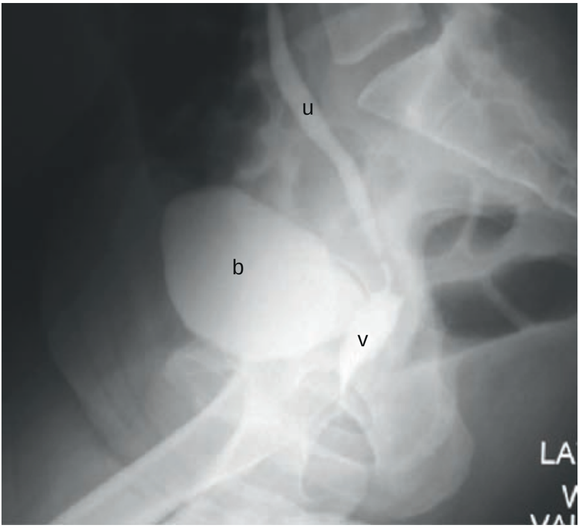

FIGURE 12-3 Antegrade nephrostogram demonstrating ureteral dilation and drainage into the vagina following abdominal hysterectomy. Contrast is seen entering the vagina **(V)** from the ureter **(U),** confirming the diagnosis of ureterovaginal fistula. A simultaneous cystogram demonstrates the bladder (**B,** bladder).

## DIFFERENTIAL DIAGNOSIS

***Differential diagnosis of a ureterovaginal fistula includes:***

Stress incontinence
Urgency incontinence
Overflow incontinence
Complete gravitational incontinence
Vesicovaginal fistula (VVF)
Urethrovaginal fistula
Vesicouterine fistula
Peritoneal fluid leak

## THERAPY

1. Ureteral stenting (see above)
2. Percutaneous drainage and possible antegrade stenting: **Percutaneous drainage and a course of antibiotic therapy are indicated prior to definitive repair if high-grade partial obstruction exists in the setting of sepsis.** If retrograde

stenting is unsuccessful but the pyeloureterogram shows continuity of the ureteral lumen, then an attempt at antegrade stenting may be undertaken.

3. Surgery: When stenting is unsuccessful and the fistula is located **distally**, ureteroneocystostomy (ureteral reimplantation, with or without psoas hitch and Boari flap) is performed. The psoas hitch maintains the anatomic position of the bladder. It is not necessary to excise the distal ureteral segment or even close the fistula unless vesicoureteral reflux is present. Fistulas located in the **middle third of the ureter** may be amenable to ureteroneocystostomy in conjunction with a Boari flap advancement from the bladder. A **proximal fistula** requires resection of the involved portion of the ureter, proximal and distal mobilization, and primary ureteroureterostomy over a stent.
4. Fistulas resulting from advanced pelvic malignancy may best be treated by urinary diversion.

## Urethrovaginal Fistula

### ETIOLOGY

Urethrovaginal fistulas are usually postsurgical (urethral diverticulectomy, antiincontinence surgery, etc.), although they may occur as a result of trauma, instrumentation (catheterization), radiation, and childbirth.

### PRESENTATION

Urethrovaginal fistulas are often asymptomatic if located in the distal third of the urethra (beyond the continence mechanism); otherwise the presentation is similar to VVF. Occasionally, these patients may present with symptoms suggestive of stress or urgency incontinence, and cystourethrography will be necessary to make the diagnosis. Dyspareunia or recurrent urinary tract infections (UTIs) are sometimes seen.

### EVALUATION

1. Voiding cystourethrogram (VCUG): Voiding images must be obtained in patients with a competent bladder neck and proximal sphincteric mechanism, or the fistula will not be demonstrated.

2. Cystoscopy: Useful to evaluate for concurrent abnormalities of the bladder and urethra, specifically the presence of any mesh material from prior sling and residual urethral diverticulum.

### DIFFERENTIAL DIAGNOSIS

***Differential diagnosis of a urethrovaginal fistula includes:***

Stress incontinence
Urgency incontinence
Overflow incontinence
Complete gravitational incontinence
Vesicovaginal fistula (VVF)
Ureterovaginal fistula
Vesicouterine fistula
Peritoneal fluid leak

### THERAPY

1. Catheter drainage may be useful in a limited number of cases if the fistula is noted promptly following the causative event.
2. Transvaginal surgical excision of any foreign body material with concomitant urethral reconstruction, multiple layer closure using periurethral fascia, a labial fat pad (Martius flap), and vaginal wall flaps is usually highly successful.

## Enterovesical Fistula

### GENERAL CONSIDERATIONS

Enterovesical fistulas may form between any segment of bowel in the pelvis (colon, ileum, etc.) and the bladder.

### ETIOLOGY

The **most common cause** of enterovesical fistula is **diverticular disease of the colon (50% to 70%).** Other common causes include neoplastic disease (colon cancer), inflammatory bowel disease (Crohn disease), radiation therapy, and trauma.

### PRESENTATION

1. Enterovesical fistula may present with recurrent UTIs, fecaluria, pneumaturia, and hematuria. Presentation with sepsis or GI symptoms is rare.

2. Gouverneur syndrome (suprapubic pain, urinary frequency, dysuria, and tenesmus) is the hallmark of enterovesical fistula.

## EVALUATION

1. **Charcoal test:** The oral administration of activated charcoal may confirm the diagnosis of enterovesical fistula. Several hours after ingestion, flecks of charcoal may be noted in the urine.
2. Cystoscopy and possible biopsy: Endoscopic visualization has a very high yield for the identification of enterovesical fistula.
   a. Eighty percent to 100% of cases demonstrate bullous edema, erythema, or exudation of feculent material from the fistula site.
   b. Generally, colonic fistulas occur on the left side and dome of the bladder, whereas small bowel fistulas occur on the dome and right side of the bladder.
   c. Biopsy of the fistula is indicated in cases in which malignancy is suspected.
3. Colonoscopy/barium enema: Although less common than diverticular disease, primary intestinal malignancy should be excluded as the cause for the fistula.
4. CT or MRI: Air in the bladder in the absence of prior lower urinary instrumentation (cystoscopy, catheterization, etc.) is highly suggestive of an enterovesical fistula. CT scan with oral or rectal contrast is generally considered to have the best diagnostic yield.
   a. **The triad of findings on CT** that are suspicious for colovesical fistula consist of bladder wall thickening adjacent to a loop of thickened colon, air in the bladder (in the absence of previous lower urinary manipulation), and the presence of colonic diverticula.
5. VCUG may demonstrate the fistulous connection. In some cases, however, the fistula may act as a “flap valve” and contrast will not be seen entering the bowel.

### DIFFERENTIAL DIAGNOSIS

Air in the bladder can also be seen secondary to urinary tract infection (UTI) with gas-forming bacteria. Debris in the bladder may be the result of a foreign body, stone or rectourethral fistula.

### THERAPY

1. **Bowel rest and hyperalimentation** (total parental nutrition [TPN]) may allow the spontaneous closure of some enterovesical fistulas.
2. **Medical therapy:** This is most applicable in enterovesical fistula secondary to Crohn disease. Appropriate use of TPN, corticosteroids, sulfasalazine, and antibiotics may promote spontaneous resolution.
3. **Surgery:** The application of surgery may involve either **a one-stage or a two-stage approach,** depending on the presence or absence of inflammation, malignancy, and adjacent organ involvement. In those cases managed in two stages, temporary fecal diversion is performed at the time of fistula repair. **Patients with an inflammatory cause of the fistula, but without gross contamination, can be treated with a one-stage procedure**, whereas those with unprepared bowel, gross contamination, or abscess may require a two-stage procedure.
   a. The surgery involves an abdominal approach, laparoscopically or open, separation of the bladder from the bowel, excision of the fistula tract, primary closure of the urinary tract, and either resection and reanastomosis of the involved bowel segment or a creation of a temporary ostomy.
   b. In some cases, partial cystectomy may be necessary.
   c. Interposition of well-vascularized tissue such as omentum between the bowel and bladder may promote healing and prevent recurrence.
   d. The second stage of surgery involves reconstitution of bowel continuity once the fistula has healed.

## Rectourethral Fistula

### ETIOLOGY

Rectourethral fistulas (RUFs) occur following radical prostatectomy, external beam radiotherapy for pelvic malignancy, pelvic brachytherapy or cryotherapy, inflammatory diseases of the pelvis (e.g., prostatic abscess, Crohn disease), or following penetrating pelvic trauma.

1. During radical prostatectomy, the anterior rectal wall may be injured during dissection of the apical portion of the prostate. A postoperative RUF may form from the reconstructed vesicourethral anastomosis to the injured portion of the rectum. In the setting of radical prostatectomy, a prior history of pelvic radiation therapy, rectal surgery, or transurethral resection of the prostate (TURP) is associated with an increased risk of RUF.

## PRESENTATION

A rectourethral fistula may present with recurrent UTIs, fecaluria, pneumaturia, or, rarely, urine per rectum. A defect may be palpable at the level of the vesicourethral anastomosis. If a Foley catheter is indwelling, it may be palpable on rectal exam.

## EVALUATION

1. Voiding cystourethrography will demonstrate a fistula between the rectum and urethra.
2. Intravenous or CT urography may be utilized if there is concern for ureteral injury.
3. Barium enema may be helpful to rule out concurrent colonic malignancy.
4. Cystoscopy and/or colonoscopy will visualize size, location, and extent of tissue involvement.
5. CT or MRI may be utilized to evaluate for inflammatory collections or other pelvic masses (e.g., malignancy).

## THERAPY

Many approaches have been advocated for repair of this complex problem. Often, however, despite successful repair of the fistula and reconstitution of the GI and genitourinary (GU) tracts, the patient may have severe problems with urinary and fecal incontinence postoperatively and should be counseled regarding this possibility prior to attempted repair. Both two-stage and one-stage repairs have been advocated, although most authors would agree that fecal diversion should be performed as an initial measure. In two-stage repairs, the GI tract is reconstituted only after the fistula has been repaired. **Surgical options** include:

1. Colostomy and urethral catheter drainage: An attempt at fecal diversion and urethral drainage is a reasonable option in most patients, especially if recognized early. With prolonged fecal diversion, the fistula may close over the urethral catheter.
2. Colostomy followed by a combined abdominal and/or perineal approach: The rectum is separated off of the urethra, and both are closed primarily. Well-vascularized tissue, such as omentum or a dartos flap, is interposed between the layers.
3. Colostomy followed by a transrectal approach (York-Mason or transsphincteric approach): The fistula is exposed, using either anal dilation and a speculum or transection of the anal sphincters. The fistula is then repaired in multiple layers by advancement and rotation of rectal wall flaps.

## Other Urinary Fistulas

### UROVASCULAR FISTULAS

**Most commonly** these fistulas occur between **the ureter and surrounding blood vessels** such as the iliacs. **Vigorous hematuria in the setting of indwelling stents in a previously irradiated patient or a patient with a history of vascular surgery should alert the physician** to the possibility of this type of fistula. If the patient is in extremis (exsanguinating, etc.), immediate surgical intervention is indicated. If the patient is stable, imaging studies, including CT, MRI, or angiography, may be indicated. In some cases, surgery may be avoided with the use of interventional radiologic techniques.

### VESICOUTERINE FISTULA

These rare fistulas most commonly occur following low-segment caesarean section. They may present with **Youssef syndrome:** Menouria, apparent amenorrhea, patent cervix, and urinary continence. Treatment is usually surgical and involves either hysterectomy and closure of the bladder (if the patient has completed childbearing) or excision of the fistula tract and separate closure of the bladder and uterus with interposition of omentum. Occasionally, successful treatment has been seen with hormonal induction of amenorrhea and catheter drainage.

## CLINICAL PEARLS

1. Diagnosis and localization of urinary tract fistulae and evaluation of concomitant injury or pathology generally involves the use of VCUG, urography (intravenous, CT, or retrograde pyelography) or other cross-sectional imaging, with or without endoscopic evaluation.
2. Effective conservative management of urinary tract fistulas with maximal drainage and diversion of urine (and stool, when involved) may obviate the need for surgical intervention.
3. Surgical intervention for urinary tract fistulas involves multilayer, tension-free closure with interposition of well-vascularized tissue.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What is the most common cause of vesicovaginal fistula (VVF) in the United States?*
2. *What are the potential advantages and disadvantages of a transvaginal VVF repair compared to a transabdominal approach?*
3. *What diagnostic studies are indicated in the evaluation of urinary incontinence in a 45-year-old woman 6 months after radical hysterectomy and radiation therapy for cervical carcinoma?*
4. *What are the most common causes for colovesical fistula and what are the indications for a two-stage versus one-stage repair?*
5. *Describe the diagnostic evaluation and subsequent management of a suspected rectourethral fistula following radical prostatectomy.*

### SUGGESTED READINGS

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## CHAPTER 13

# Nocturia

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## Introduction

This chapter will discuss the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of nocturia in adults and will act as an aid in the evaluation and treatment of patients with nocturia.

## Definitions

The International Continence Society defines nocturia as a urinary storage symptom with the complaint that the individual has to wake one or more times at night to void, with each void being preceded and followed by sleep. Though conceptually easy to use, this definition disregards the clinical relevance of nocturia. By including factors such as bother, impact, or severity of nocturia, the definition might more clearly elaborate the point at which nocturia becomes clinically relevant to evaluate and treat. Regardless of the current definition, a single episode of nocturia should not be disregarded if the patient reports being adversely affected.

## Pathophysiology

### PHYSIOLOGY

In normal adults lacking nocturia, the volume of urine excreted by the kidneys at night is less than the functional bladder capacity. Because of this, adults can normally sleep without having to wake up and void. This pattern is established during childhood and is thought in part to be related to the diurnal arginine vasopressin control mechanism. **Therefore, for successful urine storage at night, urine needs to be produced and stored in a bladder**

# Epidemiology

## PREVALENCE

Population-based studies examining the prevalence of nocturnal voids have shown that 12.5% of men and women from ages 18 to 79 report having at least two voids per night, and up to 40% of the population reports at least one void per night. It is clear that the prevalence of nocturia increases with age and becomes very common in the elderly population. Although the prevalence is greater in young women compared to young men, it increases more strongly with age in men, possibly due to prostatic obstruction in older men or increased sensitivity to arginine vasopressin in women. Several studies suggest an increased prevalence of nocturia in African American men and women compared to other ethnic groups. In an Internet-based survey in the United States, nocturia (at least two voids per night) was reported by 20% of white men, 25% of white women, 25% of Hispanic men, 27% of Hispanic women, 29% of black men, and 37% of black women. Much less is known about ethnicity and nocturia outside of the United States.

## INCIDENCE

Little is known about the incidence and natural history of nocturia (particularly in younger men, and women of any age) because few longitudinal studies examine this subject, defining *incident nocturia* is difficult, and nocturia fluctuates (i.e., it appears and/or resolves).

## BOTHER AND IMPACT ON QUALITY OF LIFE

Large population surveys have determined that the need to go to the bathroom is the most common reason for nocturnal awakening. **Overall, the degree of bother associated with nocturia is related to both quality and quantity of sleep but is more specifically related to initiating sleep and returning to sleep after awakening.** Nocturia has been correlated with daytime fatigue, morbidity, mortality, and decreased quality of life, primarily from sleep disturbance. Although correlation of nocturia with bother and quality of life is clear, causation may not be because insomnia or depression can contribute to interrupted sleep, often followed by a nocturnal void; and snoring, sleep apnea episodes, and leg movements, any of which may disrupt sleep, are associated with nocturia.

Determining the number of episodes of nocturnal voids that have an impact on bother and quality of life is essential for evaluating patients. As a generalization, studies suggest that two or more voids per night constitute clinically relevant nocturia, affecting quality of life and perceived health. It has been shown that a single episode of nocturia per night does not have the same detrimental impact on quality of life and perceived health. Although the correlation between nocturia and bother has been defined, there is no definitive distinction regarding how much reduction in nocturia frequency is necessary to relieve said bother. **This problem accentuates the difficulty in evaluating effectiveness of nocturia therapies.**

## IMPACT OF NOCTURIA: FALLS, FRACTURES, MORTALITY, AND PRODUCTIVITY

Nocturia has been associated with increased morbidity and mortality primarily through two mechanisms. First, lack of sleep alters carbohydrate metabolism and endocrine function and is ultimately associated with diabetes. Secondly, nocturia has been associated with higher risk of falls, fractures, and mortality. In elderly populations, falls comprise the greatest risk factor for fractures. The literature suggests that patients with at least two voids per night could have around twice the risk of fractures and mortality. The increased risk of mortality may be an effect of the falls and fractures resulting from middle-of-the-night void attempts, or, alternately, nocturia could simply be an indication of increasing frailty.

Increased risk of mortality is not limited to the elderly because some studies show an increase in mortality risk in younger men and women (younger than 65 years). Specifically, the Third National Health and Nutrition Examination Survey (NHANES III) found an association between increased mortality risk and two or more voids per night in men and women without comorbid conditions (e.g., heart disease, diabetes). This could imply that nocturia is actually a marker of impending morbidity (e.g., cardiovascular disease, diabetes), which is supported by studies showing a connection between nocturia and chronic illnesses.

A few select studies have also examined the impact of nocturia and loss of sleep on productivity in both the workplace and in non–work-related activities. A clear link exists between nocturia and both daytime fatigue and reduced vitality. One particular Swedish study demonstrated that adults with one or more voids per night had impaired work and non-work activity productivity.

**of adequate capacity to accommodate the volume presented during that defined period.**

## ETIOLOGY

Nocturia has a multifactorial etiology, which often is not urological in origin. The pathophysiology of nocturia can be divided into two broad categories: Primary and secondary nocturia.

1. Secondary nocturia can be described as waking up for reasons other than the need to pass urine and feeling the desire to void once awake.
2. Primary nocturia can be divided into four broad categories (Table 13-1):
   a. Reduced bladder capacity throughout the 24-hour period (e.g., maximum voided volume less than 200 mL) or exclusively at night (e.g., nocturnal bladder capacity less than 200 mL)
   b. 24-hour global polyuria characterized by excessive urine production during both day and night. Polyuria is present when 24-hour urine volume exceeds 40 mL/kg.

TABLE 13-1 **Potential Causes or Associated Risk Factors for Nocturia**

| | |
|---|---|
| Bladder storage problems | • Reduced functional bladder capacity (i.e., extrinsic compression from uterine fibroids, urogenital prolapse, ovarian mass)<br>• Bladder pain syndrome (BPS)<br>• Benign outlet obstruction (i.e., benign prostatic hyperplasia [BPH], benign prostatic obstruction [BPO])<br>• Nocturnal detrusor overactivity<br>• Neurogenic bladder<br>• Cancer of bladder, prostate, or urethra<br>• Learned voiding dysfunction<br>• Bladder or ureteric calculi<br>• Detrusor overactivity (idiopathic or neurogenic)<br>• Overactive bladder (OAB)<br>• Voiding problems and postvoid residual (PVR) urine (e.g., as a result of urogenital prolapse, urethral stricture, detrusor failure)<br>• Urogenital aging (i.e., atrophy caused by estrogen deficiency) |

*(Continued)*

TABLE 13-1 **Potential Causes or Associated Risk Factors for Nocturia—Cont'd**

| | |
|---|---|
| 24-hour polyuria | • Diabetes mellitus (DM)<br>• Diabetes insipidus (DI)<br>• Primary polydipsia |
| Nocturnal polyuria | • Congestive heart failure<br>• Obstructive sleep apnea<br>• Peripheral edema (i.e., venous stasis, hepatic failure)<br>• Excessive evening fluid intake<br>• Circadian defect in secretion or action of arginine vasopressin |
| Sleep disturbance and primary sleep disorders | • Insomnia<br>• Sleep apnea<br>• Periodic leg movements<br>• Narcolepsy<br>• Arousal disorders (i.e., sleepwalking, nightmares) |
| Other potential factors | • Medical disorders<br>  • Chronic obstructive pulmonary disease<br>  • Endocrine disorders<br>• Neurological conditions<br>  • Parkinson disease<br>  • Dementia<br>  • Epilepsy<br>• Psychiatric conditions<br>  • Depression<br>  • Anxiety<br>• Chronic pain disorders<br>• Alcohol or drug use (consumption or withdrawal)<br>• Medications (i.e., corticosteroids, diuretics, beta-adrenergic antagonists) |

(From Weiss JP, Blaivas JG, Bliwise DL, et al: The evaluation and treatment of nocturia: a consensus statement. *BJU Int* 108(1):6-21, 2011.)

c. Excessive urine production only at night (nocturnal polyuria) in the setting of normal 24-hour urine production is defined as nocturnal urine output exceeding 20% of the total 24-hour urine output (i.e., nocturnal polyuria index, NPi) in the young (age 21 to 35) and exceeding 33% of total 24-hour output in older persons.

   d. Combinations of the above, otherwise known as *mixed etiology*, which requires a multidisciplinary approach to diagnosis and treatment.

## RISK FACTORS

1. Conditions
   a. Benign prostatic obstruction (BPO): Lower urinary tract symptoms (LUTS) suggestive of BPO are well-recognized risk factors for nocturia. While up to 50% of subjects with benign prostatic enlargement (BPE) report more than two voids per night, only 33% of men with nocturia have BPE; hence BPE causing nocturia may be overestimated. Studies have shown that nocturia is the least specific LUTS associated with BPO and is the most persistent LUTS following prostate surgery.
   b. Depression: Research suggests that patients with major depression report more nocturia than those without. Furthermore, both major depression and selective serotonin reuptake inhibitors (SSRI) therapy are associated with an increased prevalence of nocturia.
   c. Hypertension and coronary artery disease: Although it has been suggested that nocturia and essential hypertension may be part of the same pathophysiological process, the connection between nocturia and hypertension is still unclear. Nocturia is associated with calcium channel blockers in women and with combination therapy, adding loop diuretics, in men. Furthermore, coronary artery disease is related to nocturia, but this association is more significant in women than in men.
   d. Neurologic diseases: Nocturia is clearly associated with multiple sclerosis, Parkinson disease, and cerebrovascular accidents. Furthermore, nocturia is three times more likely in patients with restless leg syndrome, but whether or not this is related to disturbed sleep is still unclear.
   e. Menopause and hormonal therapy: Menopause is associated with nocturia, though sleep disturbances, which often occur during menopause, may contribute. Menopausal hormone replacement therapy does not improve nocturia.

   f. Nocturnal polyuria: Multiple factors may contribute to nocturnal polyuria, including congestive heart failure, "third spacing" (from nephrosis or venous stasis), or late-night diuretic administration. Possible other pathways include impaired renal concentrating capacity, dysrhythmia of antidiuretic hormone secretion, and increased secretion of atrial natriuretic peptide.
   g. Obesity and diabetes: Several studies show that obesity can lead to as much as a three-fold risk of nocturia. Untreated diabetes mellitus (DM) is also clearly associated with nocturia.
   h. Overactive bladder (OAB) and detrusor overactivity: OAB syndrome is a symptom-defined condition characterized by urinary urgency with or without incontinence. Urinary urgency is the hallmark of OAB, which certainly includes nocturia/nocturnal urgency.
   i. Pelvic surgery: Overall, the results of studies are inconsistent regarding nocturia and hysterectomy. Surgery for stress urinary incontinence is not associated with nocturia.
   j. Prostate cancer: Whether or not LUTS are suggestive of prostate cancer is still unclear. LUTS severity is associated with the subsequent diagnosis of localized prostate cancer but not with advanced or fatal disease. Additionally, 70% of men with prostate cancer have reported at least two voids per night, whereas 7% of men with nocturia report a history of prostate cancer.
2. Lifestyle
   a. Coffee and alcohol: Although most treatment guidelines recommend decreasing bedtime fluid intake, especially coffee and alcohol, no studies have demonstrated a relationship between nocturia and alcohol or caffeine consumption.
   b. Smoking: Most studies have not found an association between nocturia and smoking, but some studies have conflicting results.
   c. Exercise: Physical activity is known to be protective of LUTS in men; exercise programs improve nocturia.
3. Race and ethnicity: Black men and women are more likely to report nocturia, but overall the association of nocturia with race and ethnicity is unknown.

## Assessment

An extensive medical history should be supplemented with a physical exam and investigations, including both a LUTS questionnaire and a bladder diary (BD). **The importance of BDs cannot be understated; they are essential in identifying the underlying pathology.**

### HISTORY

1. Duration, severity, and degree of bother of nocturia
2. Age
3. Duration and severity of other LUTS
4. Recurrent (UTIs), pelvic surgery, or radiotherapy
5. Sleep disorders (obstructive sleep apnea [OSA], insomnia, restless leg syndrome, periodic limb movement syndrome)
    a. An important clinical distinction is whether the desire to urinate wakes the patient or if the patient wakes for other reasons and subsequently voids before returning to sleep.
    b. Some OSA patients may not be aware of this problem, so it is wise to ask their bed-sharing partner about breathing interruptions or snoring.
6. Diabetes insipidus (DI), DM
    a. Demonstrated to be causes of global polyuria caused by secondary polydipsia, where excessive fluid loss causes thirst.
7. Schizophrenia, anxiety disorder
    a. Predisposition to primary polydipsia, which can lead to polyuria.
8. Cardiac failure
9. Chronic kidney disease
10. Chronic pain disorder
11. Medications
    a. Diuretics
    b. Calcium channel blockers
    c. Selective serotonin reuptake inhibitors (SSRIs)
    d. CNS stimulants
    e. Psychotropics
12. Alcohol and caffeine use

### PHYSICAL EXAM

1. Peripheral edema
    a. Pedal edema is a risk factor for nocturnal polyuria.

2. Abdominal examination
    a. An enlarged bladder caused by chronic retention may be evident on abdominal exam.
3. Plantar reflexes
4. Pelvic examination for women
    a. Check for pelvic organ prolapse.
5. Digital rectal exam (DRE) for men
    a. Check for prostatic diseases (e.g., BPE).

## INVESTIGATIONS

Urinalysis should be performed, and urinary diaries should be recorded. Simple blood tests and questionnaires are optional but recommended. Other investigations should be used when indicated by medical context. The ideal outcome tool would encapsulate: Number of nighttime voids, proportion of nights affected, nighttime voided volume, maximum voided volume (MVV), patient perception of why he or she awoke, whether the patient can fall back asleep, bother, and quality of life (QOL).

1. Urinary charts and diaries
    a. The following parameters should be attained from urinary diaries:
        1) 24-hour urine volume
        2) Daytime and nighttime frequency
        3) Maximum voided volume (MVV)
        4) Nocturnal MVV
        5) Nocturnal urine volume (NUV, the sum of the volume of all voids during sleeping time, and the volume of the first morning void)
        6) Nocturnal polyuria index (NUV as a percent of total 24-hour volume)
        7) Bedtime and time of awakening
        8) Nocturia index (Ni: NUV/MVV: If greater than 1, nocturia is owing to nocturnal urine production in excess of bladder capacity.)
        9) Nocturnal bladder capacity (NBCi): Actual minus predicted number of night voids (PNV, Ni-1): Higher NBCi indicates nocturic voids at volumes less than functional bladder capacity.

   b. Three approaches to recording micturition events have been described by the ICS.
      l) Micturition charts, which record the times of micturition day and night. Although these charts are simple, they have limited value clinically, collecting data restricted to the frequency of voids without volumes.
      2) Frequency volume charts (FVCs) allow patients to document the time and volume of each void, along with the time a patient goes to sleep and the time of awakening for at least 24 hours. These parameters allow exploration of the underlying conditions responsible for nocturia. FVC charts are typically sufficient for the evaluation of nocturia.
      3) BDs combine the FVC data collection with additional information required for clinical context (e.g., leakage episodes, pad usage, degree of urgency, degree of incontinence, fluid intake). Though BDs are the most clinically useful tool in evaluating LUTS, they are the most laborious and often have lower patient compliance.
2. Urinalysis: Valuable for detecting blood, protein sugar, leukocytes, or nitrates and for indicating pathologies such as UTI, malignancies, inflammatory diseases, or unrecognized DM.
3. Blood chemistry evaluation: Blood chemistry examination is optional and can be used to further investigate for chronic kidney disease, DM, and hypercalcemia.
4. Flow rate (Q): Not essential for the evaluation of nocturia alone, but can be relevant to the assessment of other LUTS.
5. Questionnaires: Validated questionnaires are recommended as tools for initial evaluation and treatment response, but are unsuitable for nocturnal voiding frequency. Questionnaires can be used to assess quality of life.
   a. Global LUTS questionnaires
      1) Lower urinary tract symptom score (LUTSS)
      2) International prostate symptom score (IPSS)
      3) Overactive bladder symptom score (OABSS)
   b. Nocturia specific questionnaire
      1) The Nocturia, Nocturnal Enuresis, and Sleep Interruption Questionnaire (NNES-Q)
      2) Nocturia Quality of Life Questionnaire (N-QoL)

6. Postvoid residual: Routine measurement of PVR has not proven to be beneficial in treating nocturia. However, treating an increase in voiding episodes because of urinary retention may help decrease nocturia, and retention could be indicative of other pathologies (e.g., bladder outlet obstruction).
7. Transabdominal ultrasonography: Although these evaluations rarely contribute to treatment strategies, they can be used in the evaluation of nocturia to examine the size and configuration of the prostate, hydronephrosis, diverticula, stones, and tumors.
8. Radiological examinations: Should only be used when indicated by medical context:
    a. Retrograde urethrography (RUG)
    b. Cystography
    c. Computed tomographic urography (CTU)
9. Cystoscopy: Should be performed when indicated by the presence of significant microscopic hematuria or other risk factors for bladder malignancy or other pathology such as radiation cystitis.

## Treatment

### CONSERVATIVE MANAGEMENT

1. Fluid restriction 4 to 6 hours before bedtime
2. Voiding immediately before bedtime
3. Avoiding caffeinated and alcoholic beverages
4. Leg elevation 4 to 6 hours prior to bedtime to mobilize third-space fluids
5. Taking diuretics midafternoon
6. Using sleep aids
7. Gentle exercise before retiring

### BEHAVIORAL MODIFICATION

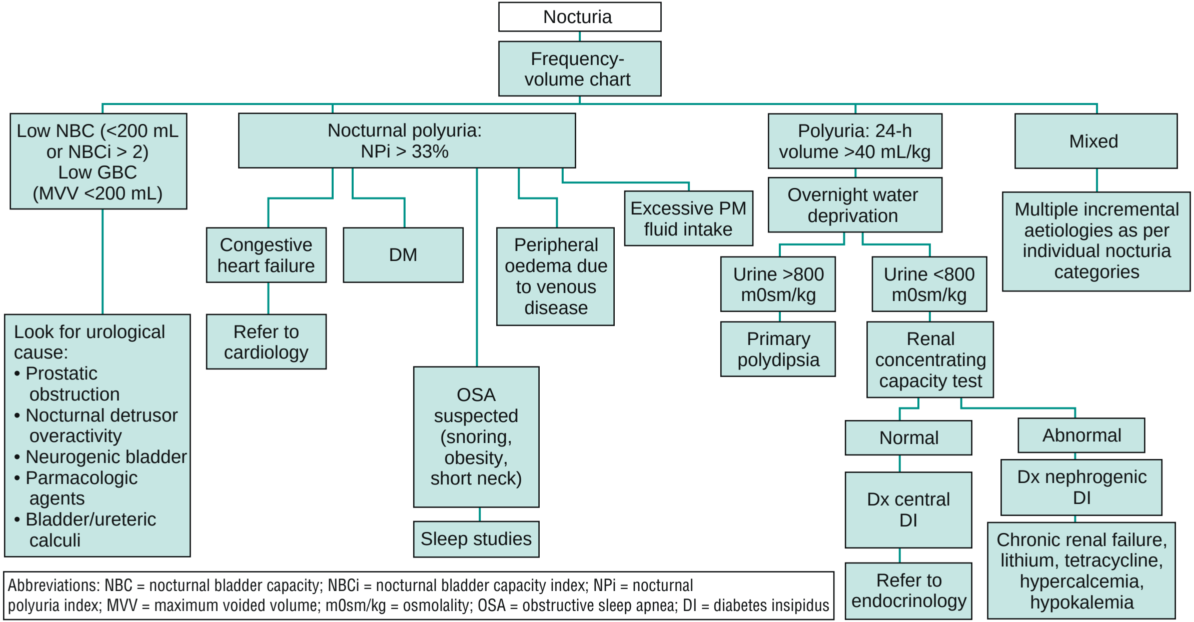
1. Biofeedback-assisted pelvic floor muscle exercises
2. Urge suppression
3. Delayed voiding techniques
4. Improved sleep hygiene
5. Decreasing caffeine, alcohol, and nighttime fluid intake

### PHARMACOTHERAPY

1. 5-alpha reductase inhibitors are thought to reduce prostate volume and diminish prostatic urethral resistance. Finasteride may reduce the number of nocturia episodes in elderly men.

Adverse effects include decreased libido, diminished ejaculate, and erectile dysfunction (ED).

2. Selective alpha-1 adrenergic antagonists relax smooth muscle in the bladder neck and urethra and reduce bladder outlet resistance. Alfuzosin, doxazosin, naftopidil, silodosin, tamsulosin, and terazosin have all been shown to reduce the number of nighttime voids in patients with BPE. Adverse effects include orthostatic hypotension, dizziness, and retrograde ejaculation.
3. Anticholinergic/antimuscarinic agents (e.g., trospium chloride, solifenacin, darifenacin, tolterodine, fesoterodine) have been shown to improve the symptoms of OAB, including detrusor overactivity, urgency, and urgency incontinence. Studies have demonstrated that anticholinergic/antimuscarinic agents significantly reduce the number of nocturnal voids. Specifically, anticholinergic agents reduce OAB-related, but not non–OAB-related, nocturnal micturitions. Moreover, this class of drugs does not improve nocturia owing to nocturnal polyuria. Adverse effects include dizziness, dry mouth, constipation, and urinary retention. They are contraindicated with urinary retention or narrow-angle glaucoma.
4. Combination therapy:
   a. The combination of alpha adrenergic antagonists and 5-alpha reductase inhibitors may be more effective than either drug used independently.
   b. The combination of antimuscarinic and alpha-1 adrenergic blockers significantly decreases the number of nocturnal voids and improves urgency, frequency, and nocturia over alpha-1 adrenergic blockers alone.
   c. Alpha-1 adrenergic blockers may be more effective at improving nocturia when given with a Phosphodiesterase Type 5 (PDE5) inhibitor.
5. Antidiuretic pharmacotherapy (Desmopressin) can be used to control nocturnal urine production caused by nocturnal polyuria. Desmopressin has been shown to decrease nocturnal diuresis and reduce nocturnal voids in a dose-dependent fashion. Desmopressin can cause clinically significant hyponatremia, requiring serum sodium testing especially when used in higher dosages. Treatment with lower doses of desmopressin has shown to minimize the risk of hyponatremia while still maintaining significant reductions in nocturnal voids. **There is evidence that women are more sensitive to the effects of desmopressin than men, suggesting the need for gender-differential dosing.**


Nocturia
Frequency-volume chart
Low NBC (<200 mL or NBCi > 2) Low GBC (MVV <200 mL)
Nocturnal polyuria: NPi > 33%
Polyuria: 24-h volume >40 mL/kg
Mixed
Look for urological cause:
• Prostatic obstruction
• Nocturnal detrusor overactivity
• Neurogenic bladder
• Parmacologic agents
• Bladder/ureteric calculi
Congestive heart failure
Refer to cardiology
DM
OSA suspected (snoring, obesity, short neck)
Sleep studies
Peripheral oedema due to venous disease
Excessive PM fluid intake
Overnight water deprivation
Urine >800 m0sm/kg
Primary polydipsia
Urine <800 m0sm/kg
Renal concentrating capacity test
Normal
Dx central DI
Refer to endocrinology
Abnormal
Dx nephrogenic DI
Chronic renal failure, lithium, tetracycline, hypercalcemia, hypokalemia
Multiple incremental aetiologies as per individual nocturia categories

Abbreviations: NBC = nocturnal bladder capacity; NBCi = nocturnal bladder capacity index; NPi = nocturnal polyuria index; MVV = maximum voided volume; m0sm/kg = osmolality; OSA = obstructive sleep apnea; DI = diabetes insipidus

**FIGURE 13-1 Algorithm for utilizing a frequency volume chart (FVC) or bladder diary (BD) to elucidate the cause of nocturia** (From Weiss JP, Blaivas JG, Blanker MH, et al: The New England Research Institutes, Inc. (NERI) Nocturia Advisory Conference 2012: Focus on outcomes of therapy. *BJU Int* 111:700-716, 2013.)

6. Diuretic pharmacotherapy can both contribute to and treat nocturia. Furosemide can reduce total nighttime voided volume associated with nocturnal polyuria when administered 4 to 6 hours prior to retiring. Bumetanide may similarly reduce the number of nocturnal micturitions.
7. Botulinum toxin has limited evidence of efficacy and is not approved for use in nocturia. However, botulinum toxin may be useful for nocturia in patients with refractory OAB and diminished bladder capacity, who have failed standard therapy.
8. NSAIDs require more evidence before they can be recommended for therapy of nocturia. However, some data shows that both loxoprofen sodium and celecoxib may reduce nocturia. The side effects of NSAIDs, such as renal injury and coagulation impairment, warrant their chronic employment in nocturia with great care.

## SURGICAL INTERVENTIONS

Surgical interventions, including transurethral resection of prostate (TURP), transurethral needle ablation (TUNA), high-intensity focused ultrasound (HIFU), visual laser ablation (VLAP), transurethral electrosurgical vaporization (TUVP), and transurethral microwave therapy (TUMT), have been used to address BPE, but very few studies look specifically at these interventions for treatment of nocturia. Performing a procedure to reduce bladder outlet obstruction (BOO) can lower the PVR volume, which may increase the amount of time taken to reach a volume at which the patient feels the need to void, in this case, during sleep hours. Regardless, nocturia does not respond as well as daytime LUTS to surgery for relief of BOO, even though the number of nocturnal micturitions may decline after TURP, TUMT, HIFU, TUNA, and TUVP. **Surgery for relief of BOO is not indicated for the management of patients with a primary complaint of nocturia unless it is clearly demonstrated that the patient has prostatic obstruction and conservative approaches have proven ineffective.** In this regard, preoperative urodynamic investigation is suggested before recommending TURP in men with nocturia as their predominant LUTS.

## PHYOTHERAPY

There are many herbal supplements marketed for treating BPH. Among these, Pygeum africanum (African plum tree) and Cernilton (rye pollen) are known to reduce the number of

TABLE 13-2 **Natural/Herbal Supplements Marketed for the Treatment of BPH**

| Species | Common Name |
|---|---|
| Serenoa repens, Sabal serrulata | American dwarf palm, saw palmetto berry |
| Pygeum africanum | African plum tree |
| Hypoxis rooperi | South African star grass |
| Urtica dioica | Stinging nettle |
| Secale cereale | Rye pollen |
| Cucurbita pepo | Pumpkin seed |

nocturnal micturitions. Serenoa repens (saw palmetto), however, does not improve nocturia (Table 13-2).

## CLINICAL PEARLS

1. Nocturia is highly prevalent: 12.5% of men and women from ages 18 to 79 report at least two voids per night and up to 40% of the population reports at least one void per night.
2. Nocturia has a multifocal etiology with causes that include reduced bladder capacity, 24-hour global polyuria, nocturnal polyuria, sleep disorders, or any combination of these. Accurate categorization of nocturia is essential for successful treatment outcomes. Use of the frequency volume chart (FVC) is the mainstay for diagnosis of the etiology of nocturia.
3. A variety of strategies exists for the treatment of nocturia. Conservative management and behavioral modification have proven to be effective. Furthermore, there is a role for 5-alpha reductase inhibitors, alpha-1 adrenergic antagonists, antimuscarinic agents, timed diuretics or antidiuretic agents, and surgical outlet reduction in appropriately selected cases.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What risk factors are associated with nocturia?*
2. *List the major consequences of nocturia.*
3. *What clinical investigations are essential for completely evaluating nocturia in a patient?*
4. *Create an algorithm for using a frequency volume chart (FVC) to evaluate the causes of nocturia.*
5. *List and describe treatment strategies for nocturia.*

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## CHAPTER 14

# Lower Urinary Tract Function and Dysfunction; Urinary Incontinence

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## Introduction

The **lower urinary tract (LUT) functions as a group of interrelated structures with a joint function in the adult to bring about efficient and low-pressure bladder filling, low-pressure urine storage with perfect continence, and periodic complete voluntary urinary expulsion, again at low pressure.** Because in the adult the LUT is normally under voluntary neural control, it is clearly different from other visceral organs, which are regulated primarily by involuntary mechanisms.

**For description and teaching, the micturition cycle is best divided into two relatively discrete phases: bladder filling/urine storage and bladder emptying/voiding.** The micturition cycle normally displays these two modes of operation in a simple on-off fashion. The cycle involves switching from activation of storage reflexes and inhibition of the voiding reflex to inhibition of the storage reflexes and activation of the voiding reflex and back again. In this chapter, we first summarize some relevant facts regarding the anatomy, neuroanatomy, physiology, and pharmacology of the LUT. We then answer certain important functional questions related to the filling and storage phase and the emptying and voiding phase of micturition. Certain “rules” are formulated that must be satisfied for the LUT to function normally. By extrapolation, these rules are used as a basis for a very simple functional classification of voiding dysfunction and as a framework to understand urodynamic evaluation and the rationale for all types of treatment. The neurourologic evaluation, classification schemes for voiding dysfunction, and the more common types of neurogenic and nonneurogenic voiding dysfunction are considered, followed by a synopsis and summation of pertinent points relative to all types of treatment for filling/storage and for emptying/voiding disorders. Benign prostatic hyperplasia (BPH) and related issues are discussed in Chapter 15.

## Relevant Lower Urinary Tract Anatomy, Physiology, Pharmacology, and Terminology

### BLADDER, URETHRA, SMOOTH AND STRIATED SPHINCTER

1. The designation *LUT* includes the bladder, urethra, and periurethral striated muscle. Anatomically and embryologically, the bladder traditionally has been divided into detrusor and trigone regions. The terms *bladder **body*** and *bladder **base*** refer to a functional rather than an anatomic division of bladder smooth muscle. This is based on distinct differences in neuromorphology and neuropharmacology between the smooth muscle lying circumferentially above (body) and below (base) the level of the ureterovesical junctions. The **smooth sphincter** refers to the smooth muscle of the bladder neck and proximal urethra. This sphincter is not anatomic but physiologic and is not under voluntary control. Others refer to this area as the *internal sphincter*, the *proximal sphincter*, and, simply, the *bladder neck sphincter*. Although most would accept the facts that the proximal urethra is that portion of the LUT between the bladder neck and "urogenital diaphragm" in both genders and that it contains smooth muscle capable of affecting urethral resistance, there is virtually no physiologic or pharmacologic change that affects the smooth muscle of the most proximal urethra without also affecting the smooth muscle of the bladder neck. **Normally, resistance increases in the area of the smooth sphincter during bladder filling and urine storage and decreases during an emptying bladder contraction.** In the human proximal urethra, there is a thick, primarily longitudinal smooth muscle layer and a thinner outer

circular layer. The longitudinal layer is believed by many, but not all, clinicians to be continuous with the musculature of the bladder base. Teleologically, this arrangement is consistent with a tonic role of the circular layer in maintaining closure during filling and storage and a phasic role for the longitudinal layer in contributing to the opening of the urethra during voiding. The bladder body does not contain discrete unidirectional layers of smooth muscle as suggested by some older texts. In the bladder base, there is a more-or-less layerlike arrangement of smooth muscle, loosely organized into inner and outer longitudinal and middle circular layers. The superficial and deep layers of the trigone musculature lie on the posterior bladder-base smooth muscle.

2. The classic view of the **external urethral sphincter,** or **external sphincter,** is that of a striated muscle within the leaves of a "urogenital diaphragm" that extends horizontally across the pelvis. It is responsible for stopping the urinary stream when the command "stop voiding" is obeyed. The **striated sphincter** concept expands this definition to include intramural and extramural portions. The **extramural** portion is under voluntary control and corresponds roughly to the "classic" external urethral sphincter, **although no unbroken sheet of muscle extends across the pelvis in either male or female, and thus no true urogenital diaphragm exists.** The **intramural** portion denotes skeletal muscle that is intimately associated with part of the urethra in both sexes above the maximal condensation of extramural striated muscle, which is continuous from that level for a variable distance to the bladder neck in the female and at least to the apex of the prostate in the male, forming an integral part of the outer muscular layer of the urethra. Some call this intramural portion the ***intrinsic rhabdosphincter***. Although differences of opinion exist regarding the ultrastructure and physiologic type of striated muscle fibers at various points within the striated sphincter mechanism, there is agreement on the general concept of a **gradual increase in activity in the striated sphincter during bladder filling, maintenance with the potential of increases in this activity during bladder storage, and virtual disappearance of this activity just prior to normal emptying/voiding.**

## INNERVATION AND RECEPTOR FUNCTION

1. **Autonomic nervous system** (ANS)**:** The physiology and pharmacology of the LUT cannot be separated from those of the ANS. There are many differences between the ANS and the **somatic nervous system** (SNS), but the one easiest for clinicians to understand and remember is that the ANS includes all efferent pathways having ganglionic synapses outside the central nervous system (CNS). There are no synapses between the CNS and the motor end plates of peripheral structures (striated muscle) in the SNS.
2. **Sympathetic** and **parasympathetic:** The terms *sympathetic* and *parasympathetic* refer simply to anatomic divisions of the ANS. The **sympathetic division** consists of those fibers that originate in the thoracic and lumbar regions of the spinal cord, whereas the **parasympathetic division** refers to those fibers that originate in the cranial and sacral spinal nerves.
3. **Innervation and neuronal interaction:** The classic view of the peripheral ANS involves a two-neuron system — preganglionic neurons emanating from the CNS and making synaptic contact with cells within ganglia, from which postganglionic neurons emerge to innervate peripheral organs (Figure 14-1). This relatively simple concept is still useful for the purposes of discussion but has undergone much expansion and modification. Most autonomic innervation of the LUT actually emanates from peripheral ganglia that are at a short distance from, adjacent to, or within the organs they innervate (the urogenital short neuron system). Additionally, the efferent autonomic pathways frequently do not conform to the classic two-neuron model, as they are often interrupted by more than one synaptic relay. **For many years, the only autonomic neurotransmitters recognized were acetylcholine and norepinephrine. It has become obvious that other transmitters are involved in various components of the ANS, and a once relatively simple concept of chemical neurotransmission has been expanded to include synaptic systems that involve modulator transmitter mechanisms, prejunctional inhibition or enhancement of transmitter release, postjunctional modulation of transmitter action, cotransmitter release, and secondary involvement of locally synthesized hormones and other substances. All of these**

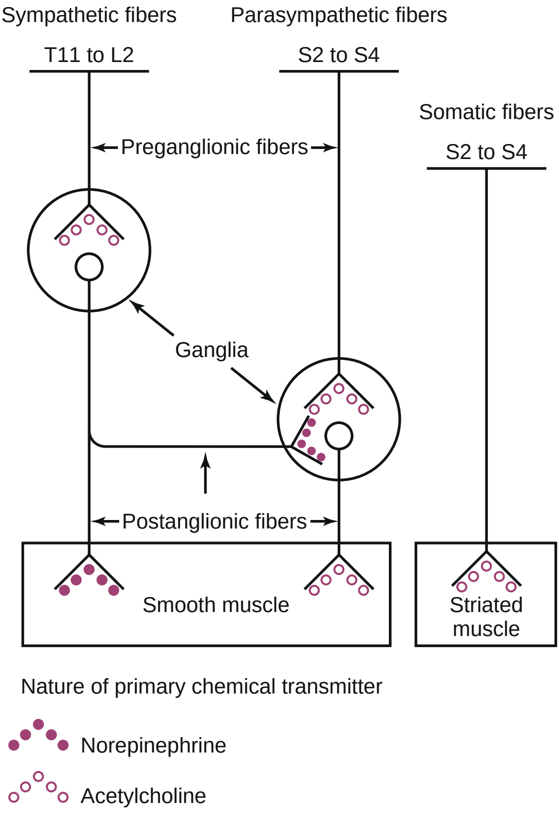

FIGURE 14-1 Classical neuroanatomic and neuropharmacologic description of the innervation of the smooth muscle of the bladder and urethra and the striated muscle of the external urethral sphincter. Note the termination of some postganglionic sympathetic (adrenergic) fibers of parasympathetic ganglion cells, providing the morphologic substrate for sympathetic inhibition of parasympathetic ganglion cell transmission. Note also the lack of ganglia in the somatic innervation. (From Hanno P, Malkowicz SB, Wein A, editors: *Clinical manual of urology,* ed 3. New York, 2001, McGraw-Hill, F14-1, p 341.)

**are subject to neuronal and hormonal regulation, desensitization, and hypersensitization.** Finally, these relationships may be altered by changes that occur secondary to disease or destruction in the neural axis, obstruction of the LUT, aging, and hormonal status.

4. **Bladder smooth muscle contraction and relaxation:** The classic model of smooth muscle contraction involves synaptic release of neurotransmitters in response to neural stimulation, with the transmitter agents subsequently combining with a recognition site, or **receptor**, on the postsynaptic smooth muscle cell membrane. The transmitter-receptor combination then initiates changes in the postsynaptic effector cell that ultimately results in what we recognize as the characteristic effect of that particular neurotransmitter on that particular smooth muscle.

   **Excitation-contraction coupling** in bladder smooth muscle has been classically described as mediated by mobilization of intracellular calcium via activation of phosphoinositide hydrolysis. The cytosolic calcium binds to calmodulin, initiating the cascade of events necessary to phosphorylate myosin and cause contraction. Relaxation is mediated by a decrease in intracellular calcium. This is accomplished by extrusion extracellularly or reuptake into intracellular stores. Smooth muscle relaxation can also be produced by causing intracellular potassium efflux, resulting in membrane hyperpolarization. Both of these latter actions are potential pharmacologic targets for decreasing bladder contractility. Unfortunately, there are no bladder-selective calcium channel blockers or potassium channel openers. Recently it has also been proposed that a main pathway for activation of bladder contraction is by calcium influx through L-type calcium channels and increased sensitivity to calcium of the contractile machinery by inhibition of myosin light chain phosphatase through activation of Rho kinase.
5. **Neurotransmitter terminology —** cholinergic and adrenergic subtypes: Clinicians are often confused because they assume that the terms *sympathetic* and *parasympathetic* imply particular neurotransmitters. These terms imply only anatomic origin within the ANS. Other adjectives are used to describe the nature of the neurotransmitter involved (see Figure 14-1).

   The term ***cholinergic*** refers to those receptor sites where acetylcholine is a primary neurotransmitter. Peripheral cholinergic fibers include somatic motor fibers, all preganglionic autonomic fibers, and all postganglionic parasympathetic fibers. The cholinergic receptor sites on autonomic effector cells are termed ***muscarinic.*** Atropine and its congeners competitively inhibit muscarinic receptor sites. Cholinergic receptor sites on autonomic ganglia and on motor end plates of skeletal muscle are designated ***nicotinic.*** These are not atropine sensitive.

The term ***adrenergic*** is applied to those receptor sites where a catecholamine is the neurotransmitter. Most postganglionic sympathetic fibers are adrenergic receptor sites, including those to LUT smooth muscle, where the catecholamine responsible for neurotransmission is norepinephrine. Adrenergic receptor sites are further classified as **alpha** (α) **or beta** (β) on the basis of the differential effects elicited by a series of catecholamines and their antagonists. Classically, the term α-***adrenergic effect*** designates vasoconstriction and/or contraction of smooth musculature in response to norepinephrine. These effects are inhibited by phentolamine, phenoxybenzamine, prazosin, and related compounds. The term β-***adrenergic effect*** implies smooth muscle relaxation in response to catecholamine stimulation and also includes cardiac stimulation, vasodilation, and bronchodilation. These effects are stimulated most potently by isoproterenol (much more so than by norepinephrine) and antagonized by multiple β-blocker compounds, of which propranolol is a prototype.

**Receptor subtyping** is a relevant concept that explains why some neurotransmitters have differing effects in different organs or anatomic localizations. Subtyping can be based on functional assays, radioligand-binding affinity, or on cloning established genotypes. For instance, there are five different muscarinic receptor subtypes ($M_1$-$M_5$). Although it appears that the majority of these in human bladder smooth muscle are of the $M_2$ subtype, bladder smooth muscle contraction is mediated primarily by the $M_3$ subtype. There are multiple subtypes of α- and β-adrenergic receptors as well. These are generally tissue specific and explain the selectivity of certain responses. The concept also underlies the development of relatively receptor subtype selective drugs for the treatment of certain LUT dysfunctions.

**Alpha-adrenergic receptors** (α-**ARs**) can be found in the detrusor smooth muscle, the vasculature, afferent and efferent nerve terminals and intramural ganglia. The predominant receptor subtypes are $\alpha_{1D}$ and $\alpha_{1a,}$ but the total $\alpha\text{-}_1$ AR expression is low, and they do not seem to have a significant role in an emptying bladder contraction. Their density is highest in the bladder base (the area circumferentially below the entrance of the ureter) posteriorly, bladder neck, and proximal urethral where they are thought to play a role in the increasing outlet resistance that occurs during bladder filling/storage.

There are three subtypes of β-ARs, the most predominant in the bladder being $\beta_{3,}$ and the response to activation is detrusor smooth muscle relaxation. Beta-adrenergic receptors (β-ARs) predominate in the bladder body (area above the ureteral entrances circumferentially) and are less dense in the base and proximal urethra.

Adding to the complexity is the fact that neurotransmitters may have no effect or differing effects at different sites (i.e., brain, pons, spinal cord, efferent ganglia, presynaptic and postsynaptic neural effector junction, sensory afferent fibers, ganglia). In this chapter, we concentrate on peripheral smooth muscle actions.

6. **Other peripheral neurotransmitters:** Other nonadrenergic noncholinergic (NANC) peripheral neurotransmitters exist in the LUT and their roles in normal and abnormal states is the object of much current investigation. These are summarized in Table 14-1. Note, however, that **the presence of a potential neurotransmitter and a laboratory tissue response to an agonist or/and antagonist does not necessarily imply physiologic function.**
7. **Peripheral innervation:** The pelvic and hypogastric nerves supply the bladder and urethra with efferent parasympathetic and sympathetic innervation, and both convey afferent sensory impulses from these organs to the spinal cord (Figure 14-2). The **parasympathetic efferent supply** is classically described as originating in the gray matter of the interomediolateral cell column of sacral spinal cord segments S2-S4. This preganglionic supply is ultimately conveyed by the **pelvic nerve.** These fibers synapse with cholinergic postganglions in the pelvic plexus or in ganglia within the bladder wall. **Efferent sympathetic fibers** to the bladder and urethra are thought to originate in the interomediolateral cell column and nucleus intercalatus of spinal cord segments T11-L2 and are carried within the **hypogastric**

TABLE 14-1 **Possible Peripheral Transmitters and Modulators in the Lower Urinary Tract**

| Transmitter (Receptor) | Effect | Site of Action |
|---|---|---|
| Acetylcholine ($M_3$) | Contraction | Bladder smooth muscle |
| Acetylcholine ($M_3$, $M_2$) | Excitation | Peripheral afferents |
| Acetylcholine ($M_2$) | Contraction | Bladder smooth muscle |
| Acetylcholine ($M_1$, $M_3$) | Contraction | Prejunctional |
| Acetylcholine ($M_2$, $M_4$) | Relaxation | Prejunctional |
| Norepinephrine ($ß_3$) | Relaxation | Bladder smooth muscle |
| Norepinephrine ($\alpha_1$) | Contraction | Bladder smooth muscle |
| Adenosine triphosphate ($P2X_1$) | Contraction | Bladder smooth muscle |
| Adenosine triphosphate ($P2X_3$) | Excitation | Peripheral afferents |
| Nitric oxide (NO) | Relaxation | Bladder base smooth muscle |
| Nitric oxide (NO) | Inhibition | Peripheral afferents |
| Serotonin ($5\text{-}HT_1$, $5\text{-}HT_2$) | Contraction | Bladder smooth muscle |
| Prostanoids | Contraction | Bladder smooth muscle |
| Prostanoids | Excitation | Peripheral afferents |
| Leukotrienes ($LTB_4$) | Contraction | Bladder smooth muscle |
| Angiotensin (AT1) | Contraction | Bladder smooth muscle |
| Bradykinin ($B_2$) | Contraction | Bladder smooth muscle |
| Endothelin (ETa) | Contraction | Bladder smooth muscle |
| Tachykinins (NK2) | Contraction | Bladder smooth muscle |
| Vasopressin (V1) | Contraction | Bladder smooth muscle |
| Vasoactive intestinal peptide ($VPAC_1$/$VPC_2$) | Relaxation | Bladder smooth muscle |
| Parathormone | Relaxation | Bladder smooth muscle |

*(Adapted from Andersson KE, Wein AJ: Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence.* Pharmacol Rev *56:581–631, 2004; Michel MC, Andersson KE, editors: Handbook of experimental pharmacology:* urinary tract, *Berlin, 2011, Springer.)*

**nerves.** Bilaterally, at a variable distance from the bladder and urethra, the hypogastric and pelvic nerves meet and branch to form the **pelvic plexus.** Divergent branches of this pelvic plexus innervate the pelvic organs. Efferent innervation of the striated sphincter is classically thought to be somatic and to emanate from the **Onuf nucleus** in sacral spinal cord segments S2-S4, exiting the spinal cord as the pudendal nerve. Some

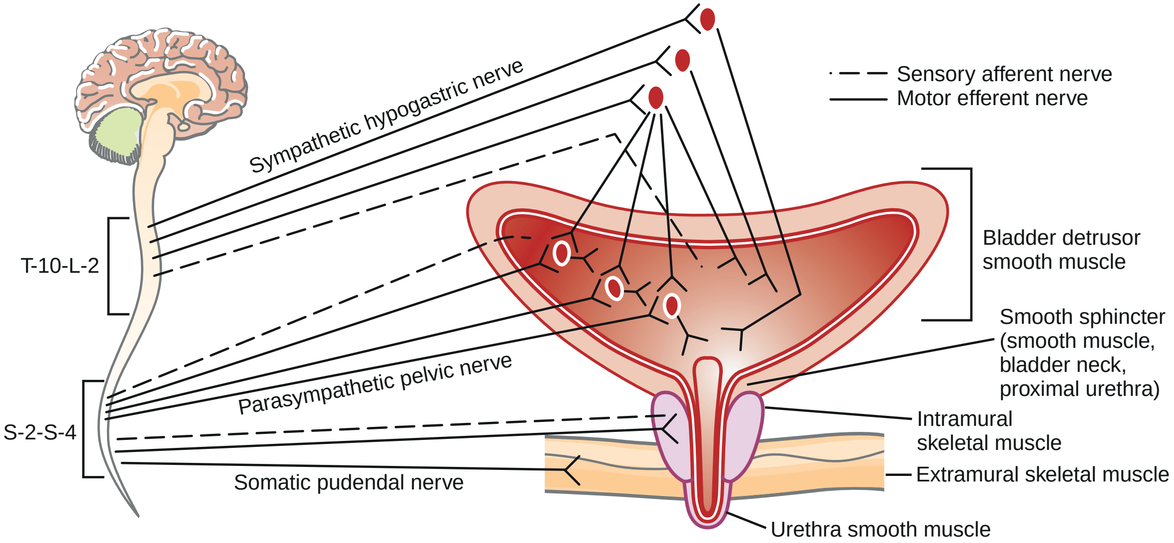
Sympathetic hypogastric nerve
Sensory afferent nerve
Motor efferent nerve
T-10-L-2
Bladder detrusor smooth muscle
Smooth sphincter (smooth muscle, bladder neck, proximal urethra)
Parasympathetic pelvic nerve
S-2-S-4
Intramural skeletal muscle
Extramural skeletal muscle
Somatic pudendal nerve
Urethra smooth muscle

FIGURE 14-2 A current conceptualization of lower urinary tract (LUT) innervation. (Adapted from Wein AJ: Pharmacologic agents for the treatment of incontinence due to overactive bladder, *Expert Opin Investig Drugs* 10:65–83, 2001.)

clinicians believe that the striated sphincter is innervated by branches of the ANS as well.

The **afferents** traveling in the pelvic nerve are primarily responsible for the initiation of the micturition reflex in the normal state. **Myelinated A-delta fibers** normally subserve this function and convey mechanoreceptor input. **Unmyelinated C fiber afferents** are more prevalent but remain relatively silent during normal filling and storage. These become "awakened" and functional under various conditions (i.e., responses to distention after spinal cord injury [SCI], to cold — the "ice water test," to nociceptive stimuli). Myelinated somatic afferents from the striated sphincter travel in the pudendal nerve. Afferents also travel in the hypogastric nerve, but little is known about their specific function. The most important afferents for initiating and maintaining normal micturition are those in the pelvic nerve, relaying to the sacral spinal cord. These convey impulses from tension, volume, and nociceptors located in the serosal, muscle, and urothelial and suburothelial layers of the bladder and urethra. In a neurologically normal adult, the sensations of filling and distention are what develops during filling/storage and initiate the reflexes responsible for emptying/voiding.

8. **Cholinergic innervation and parasympathetic stimulation:** Cholinergic innervation is abundant to all areas of the bladder of animals and humans. Although most researchers agree on the existence of a cholinergic innervation at least of the proximal urethra in animals, there is disagreement regarding the extent (and in some cases existence) of a similar innervation in humans. It is generally agreed that **abundant muscarinic cholinergic receptor sites exist throughout the bladder body and base musculature of various animal species and of humans and that they are more numerous in the bladder body. A sustained bladder contraction is produced by stimulation of the pelvic nerves, and it is generally agreed that reflex activation of this pelvic nerve excitatory tract is primarily or exclusively responsible for the emptying bladder contraction of normal micturition and for the involuntary bladder contractions seen with various neurologic and nonneurologic diseases/conditions.** Whether acetylcholine is the sole neurotransmitter released in a normal human during such stimulation is highly controversial. **Atropine resistance** refers to the incomplete

antagonism produced by atropine of the bladder response to pelvic nerve stimulation or of isolated bladder strips to electrical field stimulation (producing intramural neural stimulation). This is in contrast to atropine's ability to completely block the response of bladder smooth muscle strips to exogenous acetylcholine. It is generally agreed that atropine resistance occurs in various experimental animal models, and the most logical explanation seems to be release of additional neurotransmitter(s) besides acetylcholine in response to nerve stimulation. **Adenosine triphosphate** (**ATP**) is most commonly mentioned as the prime candidate. Normally, atropine resistance does not seem to occur in humans. However, one should not ignore the possibility that different types of atropine resistance may exist in various types of bladder overactivity, regardless of the normal state of affairs.

9. **Adrenergic innervation and sympathetic stimulation:** Adrenergic innervation of the bladder and urethral smooth musculature has been extensively demonstrated in animal studies. These studies have shown that the smooth musculature of the **bladder base and proximal urethra possesses a rich adrenergic (norepinephrine containing) innervation, whereas the bladder body has a sparse but definite adrenergic innervation.** The density of innervation seems, in all areas, to be less than that of the cholinergic systems. Considerable disagreement exists, however, as to even the presence of postganglionic sympathetic innervation in the human bladder and proximal urethra. There is general agreement that the smooth muscle of the human male bladder neck possesses a dense adrenergic innervation, but there is little consensus otherwise. Even those researchers who ascribe a significant influence on the micturition cycle to the sympathetic nervous system (SYMPNS) have difficulty demonstrating more than a sparse adrenergic innervation in other areas of the bladder and urethra. There is general agreement, however, that the smooth muscle of the bladder and proximal urethra in a variety of animals and in humans contains both α- and ß-adrenergic receptors. **Alpha-adrenergic contractile responses** predominate in the bladder base and proximal urethra, whereas **ß-adrenergic relaxation** responses predominate in the bladder body. **These are mediated primarily by the $\alpha_{1A}$ and β-3 receptor subtypes, respectively.**

Additionally, there is general agreement that, at least in certain animal models (the cat, primarily), there is a significant inhibitory influence exerted on parasympathetic ganglionic transmission by postganglionic sympathetic fibers (see Figure 14-1 and 14-2). **Those who advocate a major role of the SYMPNS in the micturition cycle summarize the influences as primarily to facilitate the filling and storage phase of micturition by three mechanisms.**

a. **Decreasing bladder contractility via an inhibitory effect on parasympathetic ganglionic transmission**
b. **Increasing outlet resistance by stimulation of the predominantly $\alpha_{1A}$ adrenergic receptors in the bladder base and proximal urethra**
c. **Increasing accommodation by stimulation of the predominantly β-3 adrenergic receptors in the bladder body**

It should be noted, however, that some researchers are of the opinion that the SYMPNS plays a very minor role in the micturition cycle in the normal human although acknowledging that the adrenergic receptors can be activated pharmacologically.

## CNS Influences on Micturition

Micturition is basically a function of the peripheral ANS. However, the ultimate control of LUT function obviously resides at higher neurologic levels. There is general consensus that a micturition "center" in the spinal cord is localized to segments S2-S4, with the major portion at S3. Early workers believed that micturition was a simple sacral spinal reflex activity that was modulated by a number of central and peripheral reflexes. It is now acknowledged that the micturition cycle is coordinated in the **pontine mesencephalic reticular formation**. Input to this area is derived from the cerebellum, basal ganglia, thalamus, hypothalamus, and cerebral cortex. Bladder contraction elicited by stimulation at or above and through this area seems to occur with a decrease in activity of the periurethral striated musculature, as in normal micturition. **In general, the tonic activity of the cerebral cortex and midbrain is inhibitory.** The regions of the cerebral hemispheres primarily concerned with bladder function are the superomedial portion of the frontal lobes and the genu of the corpus callosum. There is debate as to whether the cerebral areas controlling bladder and striated sphincter activity are geographically separate.

TABLE 14-2 **Potential CNS Neurotransmitters Other than Opioids and Their Effects on the Micturition Reflex**

| Neurotransmitter | Site | Predominant Action |
|---|---|---|
| Glutamate | Brain, SC | + |
| Glycine | Brain, SC | – |
| GABA (gamma-aminobutyric acid) | Brain, SC | – |
| Serotonin | SC | – |
| Acetylcholine | Brain | ± |
| Dopamine (D-2) | Brain | + |
| Dopamine (D-1) | Brain | – |
| Norepinephrine (α-1, α-2) | Brain, SC | ± |
| Tachykinins (NK1, NK2) | Brain, SC | + |

*CNS,* Central nervous system; *SC,* spinal cord.

Evidence exists that endogenous opioid peptides influence micturition by a tonic inhibitory effect on detrusor reflex pathways. These inhibitory effects could be mediated at several levels, including the peripheral bladder ganglia, sacral spinal cord, and brainstem micturition center. Different types of opioid receptors may be responsible at different sites for different types of effects on bladder contractility. Numerous other potential neurotransmitters can be found in various areas of the CNS. A partial list is in Table 14-2.

## Normal Lower Urinary Tract Function

### WHAT DETERMINES BLADDER RESPONSE DURING FILLING?

**The normal adult bladder response to filling at a physiologic rate is an almost imperceptible change in detrusor pressure. During at least the initial stages of bladder filling, this very high compliance (Δ volume/Δ pressure) is due primarily to passive properties of the bladder wall.** The **elastic and viscoelastic properties** of the bladder wall allow it to stretch to a certain degree without any increase in tension exerted on its contents, and at physiologic filling rates, intravesical pressure remains virtually unchanged.

In the usual clinical setting, filling cystometry shows a slight increase in detrusor pressure, but this pressure rise is a function of the fact that cystometry filling is carried out at a greater than normal physiologic rate. **Compliance can be decreased clinically by (1) any process that alters the viscoelasticity or elasticity of the bladder wall components, (2) certain types of neurologic injury or disease, and (3) filling the bladder beyond its limit of distensibility.**

The viscoelastic properties of the stroma (bladder wall less smooth muscle and epithelium) and the noncontraction of detrusor muscle account for the passive mechanical properties seen during filling. The main components of stroma are collagen and elastin. When the collagen component increases, compliance generally decreases. This can occur with various types of injury, bladder outlet obstruction (BOO), and neurologic decentralization. **Once decreased compliance occurs because of a replacement by collagen or other components of the stroma, it is generally unresponsive to pharmacologic manipulation, hydraulic distention, or nerve section.** Most often under those circumstances, augmentation cystoplasty is required to achieve satisfactory reservoir function. There may also be an active but nonneurogenic component to the filling/storage properties of the bladder. Some have suggested that an as yet unidentified relaxing factor is released from the urothelium, and others have suggested that urothelium-released nitric oxide (NO) may exert an inhibitory effect on afferent mechanisms during filling.

**At a certain level of bladder filling, spinal sympathetic reflexes are clearly evoked in all animals, and there is some indirect evidence to support such a role in humans.** An inhibitory effect on bladder contractility is thought to be mediated primarily by sympathetic modulation of cholinergic ganglionic transmission. Through this sympathetic reflex, two other possibilities exist for promoting filling and storage. One is neurally mediated stimulation of the predominantly $\alpha_{1A}$ adrenergic receptors in the area of the smooth sphincter, the net result of which would be to cause an increase in resistance in that area. The other is neurally mediated stimulation of the predominantly ß-3 adrenergic receptors in the bladder body smooth musculature, causing a decrease in tension. Good evidence also seems to support a strong tonic inhibitory effect of endogenous opioids on bladder activity at the level of the spinal cord, the parasympathetic ganglia, and perhaps the brainstem as well. Finally, bladder filling and wall distention may release autocrinelike factors, which themselves influence contractility, either by stimulation or inhibition.

## WHAT DETERMINES OUTLET RESPONSE DURING FILLING?

**There is a gradual increase in urethral pressure during bladder filling, contributed to by at least the striated sphincter element and perhaps by the smooth sphincter element.** The rise in urethral pressure seen during the filling and storage phase of micturition can be correlated with an increase in efferent **pudendal nerve** impulse frequency. This constitutes the efferent limb of a spinal somatic reflex that is initiated when a certain critical intravesical pressure is reached. This is the so-called ***guarding reflex***, which results in an increase in striated sphincter activity (see Figure 14-8).

Although it seems logical and certainly compatible with neuropharmacologic, neurophysiologic, and neuromorphologic data to assume that the muscular component of the smooth sphincter also contributes to the change in urethral response during bladder filling, it is extremely difficult to prove this either experimentally or clinically. The passive properties of the urethral wall undoubtedly play a large role in the maintenance of continence. Urethral wall tension develops within the outer layers of the urethra; however, it is a product not only of the active characteristics of smooth and striated muscle but also of the passive characteristics of the elastic collagenous tissue that makes up the urethral wall. In addition, this tension must be exerted on a soft, plastic inner layer capable of being compressed to a closed configuration — the **"filler material"** representing the submucosal portion of the urethra. The softer and more plastic this area is, the less the pressure required by the tension-producing layers to produce continence.

Finally, whatever the compressive forces, the lumen of the urethra must be capable of being obliterated by a watertight seal. This **mucosal seal mechanism** explains why a very thin-walled rubber tube requires less pressure to close an open end when the inner layer is coated with a fine layer of grease than when it is not — the latter case being analogous to scarred or atrophic urethral mucosa.

## WHY DOES VOIDING ENSUE WITH A NORMAL BLADDER CONTRACTION?

Normally, it is increased detrusor pressure producing the sensation of distention that is primarily responsible for the initiation of voluntary induced emptying of the LUT. **Although the origin of the parasympathetic neural outflow to the bladder, the pelvic**

**nerve, is in the sacral spinal cord, the actual organizational center for the micturition reflex in an intact neural axis is in the brainstem (pontine-mesencephalic formation),** and the complete neural circuit for normal micturition includes the ascending and descending spinal cord pathways to and from this area and the facilitory and inhibitory influences from other parts of the brain.

The **final step in voluntarily induced micturition** initially involves **inhibition of the somatic neural efferent activity to the striated sphincter** and an **inhibition of all aspects of any spinal sympathetic reflex evoked during filling. Efferent parasympathetic pelvic nerve activity is ultimately what is responsible for a highly coordinated and sustained contraction of the bulk of the bladder smooth musculature. A decrease in outlet resistance occurs with adaptive shaping or funneling of the relaxed bladder outlet. In addition to the inhibition of any continence-promoting reflexes that have occurred during bladder filling, the change in outlet resistance may also involve an active relaxation of the smooth sphincter through a mechanism mediated by NO.** The adaptive changes that occur in the outlet are also in part due to the anatomic interrelationships of the smooth muscle of the bladder base and proximal urethra (continuity). Other reflexes elicited by bladder contraction and by the passage of urine through the urethra may reinforce and facilitate complete bladder emptying. Superimposed on these autonomic and somatic reflexes is complex modifying supraspinal input from other central neuronal networks. These facilitory and inhibitory impulses, which originate from several areas of the nervous system, allow for the full conscious control of micturition in the adult.

## WHY DOES URINARY CONTINENCE PERSIST DURING ABDOMINAL PRESSURE INCREASES?

During voluntarily initiated micturition, the detrusor pressure becomes higher than the outlet pressure and certain adaptive changes occur in the shape of the bladder outlet with consequent passage of urine into and through the proximal urethra. Why do such changes not occur with increases in pressure that are similar in magnitude but produced only by changes in intraabdominal pressure (IAP), such as straining or coughing?

First, a coordinated bladder contraction does not occur in response to such stimuli, clearly emphasizing the fact that increases in total intravesical pressure are by no means equivalent to emptying ability. Normally, for urine to flow into the proximal urethra, not only must there be an increase in intravesical pressure but the increase must also be a product of a coordinated bladder contraction, occurring through a neurally mediated reflex mechanism and associated with characteristic conformational and tension changes in the bladder neck and proximal urethral area.

Assuming the bladder outlet is competent at rest, a major factor in the prevention of urinary leakage during increases in IAP is the fact that there is normally at least equal pressure transmission to the proximal urethra during such activity. Failure of this mechanism, generally associated with hypermobility of the bladder neck and proximal urethra (another way of describing pathologic descent with abdominal straining), is an almost invariable correlate of "genuine" stress or effort-related urinary incontinence (UI) in the female. No such hypermobility occurs in the male. The increase in urethral closure pressure that is normally seen with increments in IAP actually exceeds the extrinsic pressure increase. This indicates that active muscular function due to a reflex increase in striated sphincter activity and/or other factors such as midurethral compression that increase urethral resistance are also involved in preventing such leakage. A more complete description of the factors involved in sphincteric incontinence and its prevention can be found in the section on incontinence.

## Overview of the Micturition Cycle: Simplification and Summary

**Bladder accommodation during filling is a primarily passive phenomenon. It is dependent on the elastic and viscoelastic properties of the bladder wall and the lack of parasympathetic excitatory input. An increase in outlet resistance occurs via the striated sphincter somatic guarding reflex. In at least some species a sympathetic reflex also contributes to storage by (1) increasing outlet resistance by increasing tension on the smooth sphincter, (2) inhibiting bladder contractility through an inhibitory effect on parasympathetic ganglia, and (3) causing a decrease in tension of bladder body smooth muscle. Continence is maintained**

during increases in IAP by the intrinsic competence of the bladder outlet and urethral compression against a suburethral supporting layer. A further increase in striated sphincter activity, on a reflex basis, is also contributory during increases in IAP (e.g., by coughing or straining).

Emptying (voiding) can be voluntary or involuntary and involves an inhibition of the spinal somatic and sympathetic reflexes and activation of the vesical parasympathetic pathways, the organizational center for which is in the brainstem. Initially, there is a relaxation of the outlet musculature, mediated not only by the cessation of the somatic and sympathetic spinal reflexes but probably also by a relaxing factor, very possibly NO, released by parasympathetic stimulation or by some effect of bladder smooth muscle contraction itself.

A highly coordinated parasympathetically induced contraction of the bulk of the bladder smooth musculature occurs, with shaping or funneling of the relaxed outlet, due at least in part to a smooth muscle continuity between the bladder base and proximal urethra. With amplification and facilitation of the bladder contraction from other peripheral reflexes and from spinal cord supraspinal sources, and the absence of anatomic obstruction between the bladder and the urethral meatus, complete emptying will occur.

Whatever disagreements exist regarding the anatomic, morphologic, physiologic, pharmacologic, and mechanical details involved in both the storage and expulsion of urine by the LUT, we believe that agreement is found regarding certain points. First, the micturition cycle involves two relatively discrete processes: bladder filling/urine storage and bladder emptying/voiding. Second, whatever the details involved, these processes can be summarized succinctly from a conceptual point of view.

Bladder filling/urine storage requires the following:

1. Accommodation of increasing volumes of urine at a low intravesical pressure (normal compliance) and with appropriate sensation
2. A bladder outlet that is closed at rest and remains so during increases in IAP.
3. Absence of involuntary bladder contractions (detrusor overactivity [DO])

**Bladder emptying/voiding requires the following:**

1. **A sustained coordinated contraction of the bladder smooth musculature of adequate magnitude and duration**
2. **A concomitant lowering of resistance at the level of the smooth and striated sphincter (absence of functional obstruction)**
3. **Absence of anatomic obstruction**

**Any type of voiding dysfunction must result from an abnormality of one or more of the factors previously listed regardless of the exact pathophysiology involved. This division, with its implied subdivision under each category into causes related to the bladder and the outlet, provides a logical rationale for discussion and classification of all types of voiding dysfunction and disorders as related primarily to bladder filling/urine storage or to bladder emptying/voiding (Table 14-3 and Table 14-4). There are some types of voiding dysfunction that represent combinations of filling and storage and emptying and voiding abnormalities.** Within this scheme, however, these become readily understandable, and their detection and treatment can be logically described. **Further, using this scheme, all aspects of urodynamic, radiologic, and video urodynamic evaluation can be conceptualized as to exactly what they evaluate in terms of either bladder or outlet activity during filling and storage or emptying and voiding (see Table 14-6). Treatments for voiding dysfunction can be classified under broad categories according to whether they facilitate filling and storage or emptying and voiding and whether they do so by acting primarily on the bladder or on one or more of the components of the bladder outlet (see Tables 14-7 and 14-8).** Finally, the individual disorders produced by various neuromuscular dysfunctions can be considered in terms of whether they produce primarily storage or emptying abnormalities or a combination.

TABLE 14-3 **Functional Classification of Lower Urinary Tract Dysfunction**

| |
|---|
| **Failure to store** |
| Because of the bladder |
| Because of the outlet |
| **Failure to empty** |
| Because of the bladder |
| Because of the outlet |

TABLE 14-4 **Expanded Functional Classification of Lower Urinary Tract Dysfunction**

- I. Failure to store
  - A. Because of the bladder
    - 1. Overactivity
      - a. Involuntary contractions (detrusor overactivity [DO])
        - Neurologic disease or injury
        - Bladder outlet obstruction (BOO; myogenic)
        - Inflammation
        - Idiopathic
      - b. Decreased compliance
        - Neurologic disease or injury
        - Fibrosis
        - Idiopathic
      - c. Combination
    - 2. Hypersensitivity
      - a. Inflammatory/infectious
      - b. Neurologic
      - c. Psychologic
      - d. Idiopathic
    - 3. Underactivity (with retention and overflow incontinence)
  - B. Because of the outlet
    - 1. Stress urinary incontinence (SUI)
      - a. Lack of suburethral support
      - b. Pelvic floor laxity, hypermobility
    - 2. Intrinsic sphincter deficiency (ISD)
      - a. Neurologic disease or injury
      - b. Fibrosis
    - 3. Combination (SUI and ISD)
  - C. Combination (bladder and outlet factors)
  - D. Fistula
- II. Failure to empty
  - A. Because of the bladder (underactivity)
    - 1. Neurogenic
    - 2. Myogenic
    - 3. Psychogenic
    - 4. Idiopathic
  - B. Because of the outlet
    - 1. Anatomic
      - a. Prostatic obstruction
      - b. Bladder neck contracture
      - c. Urethral stricture, fibrosis
      - d. Urethral compression
    - 2. Functional
      - a. Smooth sphincter dyssynergia (bladder neck dysfunction)
      - b. Striated sphincter dyssynergia
  - C. Combination (bladder and outlet factors)

## Abnormalities of Filling/Storage and Emptying/Voiding: Overview of Pathophysiology (Tables 14-3 and 14-4)

**The pathophysiology of failure of the LUT to fill with or store urine adequately or to empty adequately must logically be secondary to reasons related to the bladder, the outlet, or both.**

### FILLING/STORAGE FAILURE

**Absolute or relative failure of the bladder to fill with and store urine adquately results from bladder overactivity (involuntary contraction and/or decreased compliance), decreased outlet resistance, heightened or altered sensation, or a combination.**

1. **Bladder overactivity**

   Overactivity of the bladder during filling/storage can be expressed as **phasic involuntary contractions, as low compliance, or as a combination. Involuntary contractions** are most commonly seen in association with neurologic disease or injury; however, they may be associated with increased afferent input due to inflammation or irritation of the bladder or urethral wall, BOO, stress urinary incontinence (SUI) (perhaps due to sudden entry of urine into the proximal urethra), or aging (probably related to neural degeneration), or may be idiopathic. Others have hypothesized that decreased stimulation from the pelvic floor can contribute to phasic bladder overactivity. **Decreased compliance** during filling/storage may be secondary to neurologic injury or disease, usually at a sacral or infrasacral level, but may result from any process that destroys the viscoelastic or elastic properties of the bladder wall. Bladder-related storage failure may also occur in the absence of overactivity, due to **increased afferent input** from inflammation, irritation, other causes of hypersensitivity and pain. The causes may be chemical, psychologic, or idiopathic. One classic example is bladder pain syndrome, previously and sometimes still known as *interstitial cystitis*.

2. **Outlet underactivity**

   Decreased outlet resistance may result from **any process that damages the innervation or structural elements of the**

**smooth and/or striated sphincter or support of the bladder outlet. This may occur with neurologic disease or injury, surgical or other mechanical trauma, or aging. Classically, sphincteric incontinence in the female** was categorized into relatively discrete entities: (1) **so-called genuine stress incontinence (GSI) and** (2) **intrinsic sphincter deficiency (ISD),** originally described as *type III stress incontinence*. GSI in the female was described as associated with hypermobility of the bladder outlet because of poor pelvic support and with an outlet that was competent at rest but lost its competence only during increases in IAP. ISD described a nonfunctional or very poorly functional bladder neck and proximal urethra at rest. The implication of classical ISD was that a surgical procedure designed to correct only urethral hypermobility would have a relatively high failure rate, as opposed to one designed to improve urethral coaptation and compression. **The contemporary view is that the majority of cases of effort-related incontinence in the female involve varying proportions of support-related factors and ISD. It is possible to have outlet-related incontinence due only to ISD but not due solely to hypermobility or poor support — some ISD must exist.**

**Stress or effort-related UI** is a condition that arises primarily from damage to muscles and/or nerves and/or connective tissue within the pelvic floor. Urethral support is important in the female, the urethra normally being supported by the action of the levator ani muscles through their connection to the endopelvic fascia of the anterior vaginal wall. Damage to the connection between this fascia and this muscle, damage to the nerve supply, or direct muscle damage can therefore influence continence. Bladder neck function is likewise important, and loss of normal bladder neck closure can result in incontinence despite normal urethral support. In older writings, the urethra was sometimes ignored as a factor contributing to continence in the female, and the site of continence was thought to be exclusively the bladder neck. However, in approximately 50% of continent women, urine enters the urethra during increases in abdominal pressure. The continence point in these women (highest point of pressure transmission) is at the midurethra.

**Urethral hypermobility** implies weakness of the pelvic floor supporting structures. During increases in IAP, there is descent of the bladder neck and proximal urethra. If the outlet opens concomitantly, SUI ensues. In the classic form of urethral hypermobility, there is rotational descent of the bladder neck and urethra. However, the urethra may also descend without rotation (it shortens and widens), or the posterior wall of the urethra may be pulled (sheared) open while the anterior wall remains fixed. However, urethral hypermobility is often present in women who are not incontinent, and thus the mere presence of urethral hypermobility is not sufficient to make a diagnosis of a sphincter abnormality unless UI is also demonstrated. The **"hammock hypothesis"** of John DeLancey (1994) **proposes that for stress incontinence to occur with hypermobility, there must be a lack of stability of the suburethral supportive layer.** This theory proposes that the effect of abdominal pressure increases on the normal bladder outlet, if the suburethral supportive layer is firm, is to compress the urethra rapidly and effectively. If the supportive suburethral layer is lax and/or movable, compression is not as effective. **Intrinsic sphincter dysfunction** denotes an intrinsic malfunction of the urethral sphincter mechanism itself. In its most overt form, it is characterized by a bladder neck that is open at rest and a low Valsalva leak point pressure (VLPP) and urethral closure pressure and is usually the result of prior surgery, trauma with scarring, or a neurologic lesion.

**Urethral instability** refers to the rare phenomenon of episodic decreases in outlet pressure unrelated to increases in bladder or abdominal pressure. The term *urethral instability* may be a misnomer because many believe that the drop in urethral pressure represents simply the urethral component of a normal voiding reflex in an individual whose bladder does not measurably contract because of either myogenic or neurogenic reasons. Little has appeared in the literature about this entity since the last edition of this text. It is sometimes cited as a cause of urgency and urgency incontinence but can be seen in a "normal woman."

In theory at least, categories of **outlet-related incontinence** in the male are similar to those in the female. **Sphincteric incontinence in the male is not, however, associated with hypermobility of the bladder neck and proximal urethra but is similar to what is termed *ISD* in the female.** It is seen most often after radical prostatectomy or in neurologic disease or trauma affecting the sacral spinal cord or pathways distal to this. It is seen occasionally after outlet-reducing surgery as well. There is essentially no information regarding the topic of urethral instability in the male.

The **treatment of filling/storage abnormalities** is directed toward **inhibiting bladder contractility, decreasing sensory output, mechanically increasing bladder capacity, and/or toward increasing outlet resistance, the latter either continuously or just during increases in IAP.**

## EMPTYING/VOIDING FAILURE

**Absolute or relative failure to empty the bladder results from decreased bladder contractility (a decrease in magnitude, coordination, or duration), increased outlet resistance, or both.**

1. **Bladder underactivity (underactive bladder, impaired bladder contractility)**

   Absolute or relative failure of bladder contractility may result from **temporary or permanent alteration in one of the neuromuscular mechanisms necessary for initiating, propagating, and maintaining a normal detrusor contraction. Inhibition of the voiding reflex in a neurologically normal individual may also occur; it may be by a reflex mechanism secondary to increased afferent input, especially from the pelvic and perineal areas, or may be psychogenic. Nonneurogenic causes** include impairment of bladder smooth muscle function, which may result from overdistention, ischemia, various centrally or peripherally acting drugs, or fibrosis, the latter most often due to BOO or repeated infection.
2. **Outlet overactivity or obstruction**

   Pathologically increased outlet resistance is much more common in men than in women. Although it is **most often secondary to anatomic obstruction, it may be secondary to a failure of relaxation or due to active contraction of the striated or smooth sphincter during bladder contraction. Striated sphincter dyssynergia** is a common cause of functional or nonanatomic (as opposed to fixed anatomic) obstruction in patients with neurologic disease or injury. Outlet obstruction in the male is most often due to prostatic enlargement, less commonly urethral stricture disease. A common cause of outlet obstruction in the female is compression or fibrosis following surgery for sphincteric incontinence.

The **treatment of emptying failure generally consists of maneuvers to increase intravesical/detrusor pressure, facilitate the micturition reflex, decrease outlet resistance, or a combination. If other means fail or are impractical, intermittent or continuous catheterization is an effective way to circumvent emptying failure.**

## The Neurourologic Evaluation (Table 14-5)

### HISTORY

**Symptomatology** can be valuable in suggesting whether voiding dysfunction represents an abnormality of storage, emptying, or both. A complete history of the symptoms and their onset, duration, time course, and relationship to neurologic disease or other neurologic symptoms is essential. **Incontinence** is generally a primary symptom of filling and storage failure and may be bladder or outlet related; however, it can also result from ureteral ectopy and congenital or acquired urinary fistulas. Leakage that is associated only with increases in IAP implies **SUI** at least in the female. Gravitational urethral incontinence that worsens on straining implies **ISD. Precipitous incontinence** with a more

TABLE 14-5 **Neurourologic Evaluation**

| |
|---|
| History |
| Bladder diary |
| Quality of life assessment |
| Physical examination |
| Neurologic examination |
| Urine bacteriologic studies |
| Renal function studies |
| Radiologic evaluation |
| Upper tract |
| Lower tract |
| Urodynamic/video-urodynamic study |
| Endoscopic examination |

sustained type of leakage similar to voiding is characteristic of **involuntary bladder contractions** (DO). It can occur with sensation (**urgency**) or without urgency in the absence of sensation. Incontinence is not always, however, a primary symptom of filling and storage failure. **Overflow, or paradoxical incontinence,** can develop in a patient with insidious detrusor decompensation with emptying failure. The leakage in this case is generally most prominently associated with changes in position or sudden increases in IAP and can mimic stress incontinence. **Urgency** is now defined in the International Continence Society (ICS) lexicon as a sudden compelling desire to void that is difficult to defer. **Previously the definition included "for fear of leaking."** A perceived need to void solely because of pain is generally secondary to inflammatory disease.

An **increase in daytime urinary frequency** can be psychogenic, represent a response to pain on low-volume bladder distention (usually indicative of inflammatory disease), be due to DO, or simply be due to increased fluid intake. Increased frequency can also result from emptying failure with a substantial residual urine volume and therefore a decreased functional bladder capacity. It can also exist in association with outlet obstruction-induced DO. **Nocturia** usually accompanies nonpsychogenic urinary frequency and can be associated, on the same basis as increased daytime frequency, with either storage or emptying failure. It is most commonly associated with an increased nocturnal urine output (nocturnal polyuria).

The symptom of **pressure** defies exact definition. It is not quite the urge to void but rather a feeling that the bladder is full or that the urge to void will occur shortly. There is often no discernible urodynamic dysfunction in patients who complain of this, except perhaps for hypersensitivity during filling; however, such dysfunction can be due to an elevated detrusor pressure during filling, but one that is below the level necessary to elicit the sensation of distention or urgency. This symptom also may be representative of an accurate perception of inadequate emptying with a modest or large residual urine volume. A **bladder diary** is especially useful in accurately portraying symptoms due to a filling and storage abnormality. This should include at least the following: fluid intake, time and amount of voiding, association with urgency (or not), and leakage (or not), including type and amount. The diary will also allow estimation of the functional capacity, which should serve as a guide for filling volume during urodynamics.

**Hesitancy, straining to void,** and **poor or interrupted stream** generally may reflect a failure to empty adequately, but they can occur in an individual with frequency and urgency who, on toileting, simply has difficulty initiating a voluntary bladder contraction with a small intravesical urine content.

Pain in the area of the bladder may reflect intrinsic bladder pathology (bladder pain syndrome/interstitial cystitis, malignant or premalignant conditions, infection or inflammation, calculus) or be due to an extrinsic causation (e.g., abscess, compression). A detailed **history of prior medical and surgical treatment** and the results should always be sought.

## PHYSICAL AND NEUROLOGIC EVALUATION

Findings from a **general physical examination** are nonspecific. There may be cutaneous excoriation secondary to urinary leakage. A **focused physical examination** should include the **lower abdomen, genitalia, and rectum** in men and women. **Prostate** abnormalities must be detected. A careful **pelvic examination in women** is necessary to detect the presence and degree of pelvic organ prolapse: apical, uterine, and anterior and posterior vaginal prolapse. The **neurologic examination** provides evidence of the presence or absence of a neurologic lesion and, if present, localizes it in an attempt to corroborate and explain a given LUT dysfunction. **Mental status** is determined by noting the level of consciousness, orientation, speech, comprehension, and memory. Mental status aberrations can be secondary to neurologic diseases that produce LUT dysfunction, such as senile and presenile dementia, brain tumors, and normal pressure hydrocephalus.

Cranial nerve dysfunction, except when indicative of a brainstem lesion, has little specific relevance to voiding dysfunction. Careful examination of **motor function and coordination** and a **sensory examination** (including touch, pain, temperature, vibration, and position) can have anatomic and etiologic significance. **Sensory or motor deficits** may suggest specific levels of spinal pathology, either unilateral or bilateral. The abnormalities associated with SCI, Parkinson disease (PD), multiple sclerosis (MS), and cerebrovascular diseases are usually obvious. The presence of **lateralizing signs** suggests that only one side of the neural axis is affected. **Quadriplegia** suggests an abnormality of the cervical or high thoracic spinal cord, whereas true **paraplegia** indicates a cord lesion below the upper thoracic segments. Specific **dermatomal sensory alterations or deficits** suggest localized pathology at the spinal cord or nerve root level.

Evaluation of the **deep tendon reflexes** provides an indication of segmental spinal cord function and suprasegmental function. **Hypoactivity** of the deep tendon reflexes generally is associated with a lower motor neuron (LMN) lesion (in this context, meaning from the anterior horn cells to the periphery), whereas **hyperactivity** generally indicates an upper motor neuron (UMN) lesion (between the brain and anterior horn cells of the spinal cord). These terms, *UMN* **and** *LMN*, refer, strictly speaking, only to the SNS. However, by convention, they are often applied by urologists and neurologists to the efferent portions of the ANS innervating the LUT. In this context, the terms are generally understood to mean the following: **UMN**, between the brain and anterior horn cells, and **LMN**, from anterior horn cells to the periphery, including all preganglionic and postganglionic fibers. **Commonly tested deep-tendon reflexes** include the **biceps** (C5-C6), **triceps** (C6-C7), **quadriceps or patellar** (L2-L4), and **Achilles** (L5-S2). A pathologic toe sign (**Babinski reflex**) generally indicates a somatic UMN lesion but can be absent with a complete lesion and marked spasticity. A Babinski reflex may be present contralaterally with a unilateral lesion or may be present unilaterally with a bilateral lesion. The generic term ***bulbocavernosus reflex (BCR)*** describes contraction of the bulbocavernosus and ischiocavernosus muscles after penile glans or clitoral stimulation, or stimulation of the urethral or bladder mucosa by pulling an indwelling Foley catheter. These reflexes are mediated by pudendal and/or pelvic afferents and by pudendal nerve efferents and, as such, represent a local sacral spinal cord reflex. Most clinicians would agree that the BCR reflects activity in S2-S4, but some believe that this may involve segments as high as L5. Motor control of the **external anal sphincter** (**EAS**) is variously described as being served by sacral cord segments S2-S4 or S3-S5. A visible contraction of the EAS after pinprick of the mucocutaneous junction constitutes the **anal reflex,** and its activity usually parallels that of the BCR. **EAS tone**, when strong, indicates that activity of the conus medullaris is present, whereas absent anal sphincter tone usually indicates absent conal activity. **Volitional control of the EAS** indicates intact control by supraspinal centers. The **cough reflex** (contraction of the EAS with cough) is a spinal reflex that depends on volitional innervation of the abdominal musculature T6-L1. The afferent limb is apparently from muscle receptors in the abdominal wall that enter the spinal cord and ascend. As long as one of these segments remains under volitional control, the cough reflex may be positive. If a lesion above the outflow to the abdominal musculature exists, the cough reflex is generally absent.

In regard to lesions that affect the spinal cord, it must be remembered that the **level of the vertebral lesion (such as in SCI or disk disease) usually differs from the spinal cord segmental level. Sacral spinal cord segments S2-S4 are generally at vertebral bone levels L1-L2.** Additionally, it must be remembered that after spinal cord trauma, descending degeneration of the cord may occur.

In a **complete spinal cord lesion above the conus medullaris** (otherwise known as *suprasegmental* or *UMN*), there will generally be, after spinal shock has passed, hyperactivity of the deep tendon reflexes, skeletal spasticity, and absent skin sensation below the level of the lesion; pathologic toe signs will exist. Following a **complete spinal cord lesion at or below the conus** (segmental or infrasegmental or LMN), after spinal shock has passed, there will generally be absent deep tendon reflexes, skeletal flaccidity, and absent skin sensation below the lesion level; pathologic toe signs will be absent.

## RADIOLOGIC EVALUATION

1. **Upper tracts** (see Chapter 2)

   Many urologists believe that **contrast imaging** (CT urography or intravenous urography) is the optimal screening study of the upper tracts (kidneys and ureters) in patients with significant voiding dysfunction. **Ultrasonography** (US) can give adequate information about hydronephrosis, the presence of calculi, and occasionally hydroureter. **Isotope studies** can be useful to evaluate renal blood flow and function and to establish the presence of renal or ureteral obstruction. Dilation of the ureters or renal collecting system or a decrease in function can represent significant complications of LUT dysfunction and as such are often indications for intervention. **Upper tract imaging, however, is generally recommended only in specific situations in the adult:** (1) decreased bladder compliance, (2) neurogenic LUT dysfunction, (3) severe urethral obstruction, (4) incontinence associated with significant postvoid residual, (5) coexisting loin and flank pain, (6) severe untreated pelvic organ prolapse, and (7) suspected extraurethral UI.

2. **Lower tracts**

This portion of the chapter considers only basic **cystourethrographic patterns** that relate directly to voiding dysfunction caused by neuromuscular disease. **There are only a few basic cystourethrographic radiologic configurations**, but their significance can be fully ascertained only by concomitant urodynamic study. A **closed bladder neck** is normal in a resting individual whose bladder is undergoing either physiologic or urodynamic filling. However, it can also occur in an individual with an areflexic bladder who is straining to void and in an individual in whom a micturition reflex is occurring but whose smooth sphincter area is dysfunctional or dyssynergic. The closed appearance can sometimes be mimicked to a great degree by significant prostatic enlargement with bladder neck and urethral compression as well. An **open bladder neck** is normal during voluntarily induced bladder micturition and during most involuntary bladder contractions. However, this appearance during filling/storage may also be due to ISD, seen in some types of neurologic injury or disease, or to endoscopic or open surgical alteration, and it may be seen normally in some females with GSI.

A **closed striated sphincter** is normal during physiologic or urodynamic filling and is normally seen with an attempt to stop normal urination or to abort an involuntary bladder contraction. The sphincter also normally remains closed during abdominal straining. During voluntary micturition or during micturition secondary to an involuntary bladder contraction caused by neurologic disease at or above the brainstem, the striated sphincter should open unless the patient is trying to abort the bladder contractions by voluntary sphincter contraction or detrusor sphincter dyssynergia (DSD) is present.

A cystogram in the erect position at rest and during straining may be useful in quantitating the degree of classical SUI (bladder neck closed at rest, open with straining, associated with hypermobility) versus classical ISD (bladder neck open at rest, more leakage with straining, and no hypermobility). Voiding cystourethrography is useful to diagnose the site of obstruction in a patient with proven urodynamic evidence of obstruction.

## ENDOSCOPIC EVALUATION

**Endoscopy is recommended only in specific situations in the adult with only lower urinary tract dysfunction:** (1) when initial testing suggests other types of pathology (microscopic or gross hematuria; pain, discomfort, and persistent or severe symptoms of bladder overactivity; and suspected extraurethral incontinence); (2) in patients who have previously undergone bladder, prostate, or other pelvic surgery; and (3) in men with incontinence. Bladder washings or a voided urine for cytology should be sent if symptoms suggest the possibility of neoplastic or preneoplastic changes in the bladder or urethral epithelium. The presence or absence of trabeculation (which is compatible with obstruction, involuntary bladder contractions, or neurologic decentralization) can also be determined. Endoscopic examination may be thought to be confirmatory of or exclude anatomic obstruction at a particular site, but it should be recognized that not everything that appears occlusive endoscopically is obstructive urodynamically (all large prostates are not obstructive), and lack of a visually appreciated occlusion does not exclude functional obstruction (striated or smooth sphincter dyssynergia) during bladder emptying and voiding. In describing findings on an endoscopic exam, it is better to use the term *occlusion* because *obstruction* implies urodynamic significance.

## URODYNAMIC AND VIDEO URODYNAMIC EVALUATION

1. **General** (Table 14-6)

   The studies that fall under the heading of ***LUT urodynamics*** **consist simply of methods designed to generate quantitative data relevant to events taking place in the bladder and bladder outlet during the two relatively discrete phases of micturition** described previously: filling/storage and emptying/voiding.

TABLE 14-6 **Urodynamics Simplified**

| | Bladder | Outlet |
|---|---|---|
| Filling/storage phase | Pves[1] Pdet[2] (FCMG[3])<br>DLPP[4] | UPP[5]<br>VLPP[6]<br>FLUORO[7]<br>MUPP[11] |
| Emptying phase | Pves[8] Pdet[9] (VCMG)[10] | FLUORO[12]<br>EMG[13] |
| | FLOW[14]<br>RU[15] | |

This functional conceptualization of urodynamics categorizes each study as to whether it examines bladder or outlet activity during the filling/storage or emptying phase of micturition. In this scheme, uroflow and residual urine integrate the activity of the bladder and the outlet during the emptying phase.

[1,2] Total bladder (Pves) and detrusor (Pdet) pressures during a filling cystometrogram (FCMG).
[3] Filling cystometrogram.
[4] Detrusor leak point pressure.
[5] Urethral pressure profilometry.
[6] Valsalva leak point pressure.
[7] Fluoroscopy of outlet during filling/storage.
[8,9] Total bladder and detrusor pressures during a voiding cystometrogram (VCMG).
[10] Voiding cystometrogram.
[11] Micturitional urethral pressure profilometry.
[12] Fluoroscopy of outlet during emptying.
[13] Electromyography of periurethral striated musculature.
[14] Flowmetry.
[15] Residual urine.

This conceptualization fits nicely with the concept of two phases of micturition and the description of each phase requiring three components to occur normally.

Ideally, the urodynamic (UDS) and video urodynamic (VUDS) evaluation should be able to answer the implied questions regarding the normality or abnormality of each of the components of the two phases of micturition. Combined video urodynamic or separate cystourethrographic study (referred to as FLUORO in Table 14-6) also provides information regarding the presence or absence of vesicoureteral reflux (VUR).

A **simple formulation of the commonly utilized urodynamic studies, based on the two phases of micturition concept, is presented in** Table 14-6**, the individual studies characterized as to whether they evaluate aspects of bladder or outlet activity during filling and storage or emptying.** Within this scheme, **flowmetry** and **residual urine** are simply **ways of integrating bladder and outlet activity during the emptying phase of micturition.**

The primary **purpose of UDS and VDS evaluation is threefold:** (1) determine the precise etiology(ies) of the LUT symptoms and/or dysfunction, (2) identify urodynamic risk factors for upper and lower urinary tract deterioration, and (3) identify factors that might affect the success of a particular therapy. The **study should ideally reproduce the patient's symptoms and/or accurately reflect bladder and outlet activity and sensation during filling/storage and emptying/voiding and provide a pathophysiologic basis for management.** UDS and VUDS can also be utilized along with symptomatology to assess treatment results.

**Certain very simple rules aid immeasurably in obtaining the maximum benefit from UDS and VUDS.** Although these rules sound obvious, they are often ignored, sometimes even by experienced urodynamicists. **The prime directive is that the study must reproduce the clinical symptomatology or clinical abnormality being investigated.** If it does not, then insofar as that particular patient is concerned, and despite the fact that the study may be perfectly done and the data beautifully reproduced, it may be worthless. Conversely, **the appropriate study done so as to reproduce the symptoms always yields pertinent information.** As a corollary, it is not necessary to perform the most complicated type of VDS with every patient. **The simplest, most readily reproducible, and least invasive study that gives the information desired is always the best.** The subject has become far more complicated than necessary. A large percentage of LUT dysfunction problems can be diagnosed by a logical clinician using relatively simple UDS. As the complexity of the problem and the number of failed prior therapies increases, so does the need for more complicated or combined VDSs. Finally, it must be remembered **that urodynamic and video urodynamic evaluation must be an interactive process between the patient and**

**examiner.** Information must be constantly exchanged and the study sequence tailored to a given patient and his or her LUT symptoms and signs.

2. **Flowmetry**

Flowmetry is a way to **integrate the activity of the bladder and outlet during the emptying phase of micturition.** The flow rates and pattern represent the recorded variables; if these are both normal, it is unlikely that there is any significant disorder of emptying. A normal flow, however, does not entirely exclude obstruction, which is strictly defined on the basis of a relationship between detrusor pressure and simultaneous flow. **Consistently low flow rates with adequate volumes voided generally indicate increased outlet resistance, decreased bladder contractility, or both. Flow rates considerably in excess of normal may indicate decreased outlet resistance.** There are only a few abnormal flow patterns. An abnormally broad plateau with a low mean and peak rate generally indicates outlet obstruction or decreased detrusor contractility or both. Intermittent flow is generally secondary to abdominal straining or sphincter dyssynergia, but in rare instances, it can be due to undulating low-amplitude detrusor contractions. An idealized normal flow curve is seen in Figure 14-3 and flow tracings from individuals with various characteristic abnormalities are seen in Figure 14-4.

The primary caveat in interpreting uroflow is to **make sure that the flow event closely approximates the usual voiding event for that patient. If not, it should be repeated with a comfortably full bladder.** In an adult, flow events of 100 mL or less should be interpreted with caution. An overfilled bladder may be accompanied by reduced flow rates probably because of temporary dysfunction introduced by overstretching of detrusor fibers. Measurements of only one flow parameter, such as peak flow, may be misleading because it is possible for patients with decreased outlet resistance to generate very high peak flows with straining. In comparisons of flow rates in a given individual from one time to another, either for the purposes of evaluating treatment or following a given condition, it is very important to standardize the rates to a given volume. Volume/rate nomograms can be useful in this regard. Most data from studies cite norms of 15 and 25 mL/sec for mean and maximum flow rates. However, flow rates should

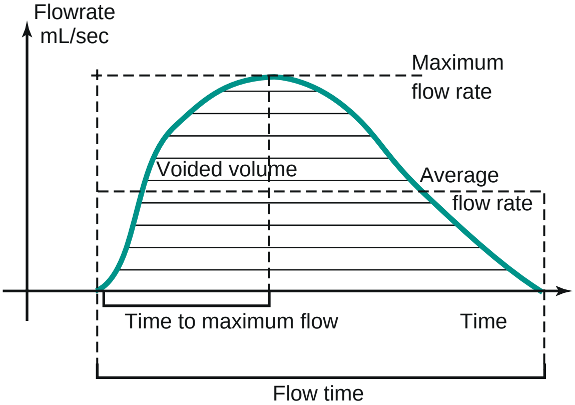

**FIGURE 14-3 Terminology of the International Continence Society (ICS) relating to the urodynamic description of urinary flow.** (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

be standardized in terms of the minimum acceptable flow rates for given gender and age groups. Most "normal" data relate to flowmetry in patients younger than the age of 55 years.

3. **Residual urine volume**

Similarly, residual volume **integrates the activity of the bladder and outlet during emptying.** It can be measured directly or estimated by cystography or US. A **consistently increased residual urine** volume that reflects the usual status of that patient generally indicates increased outlet resistance, decreased bladder contractility, or both. **Negligible residual urine volume** is compatible with normal function of the LUT but can also exist with significant disorders of filling and storage (i.e., incontinence) or emptying disorders in which the intravesical pressure is simply sufficient to overcome increases in outlet resistance up to a certain point. Generally, a significant residual urine volume is considered to be indicative of relative detrusor failure, with or without outlet obstruction. Residual urine volume may be expressed as an absolute number (mL) or as a percent of the functional bladder capacity. The amount or percentage that is "normal" or "acceptable" or "pathological" and an indication for treatment is debatable and varies with the clinical circumstances.

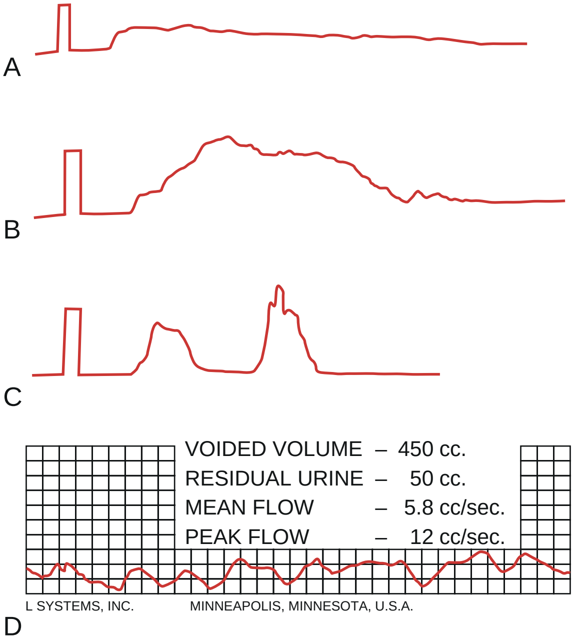

FIGURE 14-4 **A,** Flowmetry in the patient with bladder outlet obstruction (BOO). Height of bar represents a flow of 10 mL/sec. Maximum flow is generally established soon after the onset of voiding. Peak and mean flow rates are decreased. Flow time is prolonged. Note that this diagnosis cannot be made from this flow event alone. However, this is most characteristic of BOO in a patient with normal detrusor. **B,** Uroflow event from a patient with impaired detrusor contractility. Maximum flow is established near the middle of the flow event. Mean and peak flow rates are decreased. Flow time is somewhat prolonged. To establish this diagnosis beyond a doubt, especially because the therapeutic options differ, a pressure/flow study would be necessary to separate this entity from BOO. **C,** Intermittent flow. This type of intermittent flow pattern is most commonly due to abdominal straining. In such a patient with decreased outlet resistance, the peak flow rate is often normal or may even be above normal. **D,** Another type of intermittent flow pattern. This can be due either to sphincter dyssynergia or low-amplitude fluctuating detrusor contractions. With sphincter dyssynergia, the changes in flow usually occur faster and are more staccatolike. This is actually from a patient with low-amplitude fluctuating detrusor contraction. (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

4. **Filling cystometry**

Cystometry refers to the method by which changes in bladder pressure are measured. The test was designed originally to evaluate the filling and storage phase of bladder function and to measure changes in bladder pressure with slow progressive increases in volume. Strictly speaking, this is **filling cystometry,** as opposed to **voiding cystometry.** Unless the examiner clearly recognizes the distinction, erroneous conclusions regarding the activity of the bladder during the emptying phase of micturition may be made on the basis of what is commonly called a *cystometrogram* but which, in reality, represents only filling, and not voiding, cystometry. There is no single best method of performing cystometry or any urodynamic study, for that matter. All have their shortcomings. The "experts" often differ significantly in their choice of testing sequences and catheters, but their conclusions about an individual patient are usually remarkably similar. Liquid is preferred as a medium for filling cystometry. Few, if any, currently use gas (carbon dioxide). For full micturition studies (filling and voiding cystometry), a liquid medium is obviously required.

**The first sensation of bladder filling and fullness, the normal urge to void, the sensation of urgency, and the feeling of imminent micturition** are important data to record. When a **phasic involuntary detrusor contraction** occurs, **it is important to note whether this coincides with a sensation of urgency and whether suppression is possible.**

The pressure measured within the bladder is composed of that contributed by the detrusor plus IAP. Thus **any pressure increment recorded on a simple cystometrogram may at least partially, and sometimes totally, reflect IAP. To eliminate such artifactual problems, it is desirable to measure IAP simultaneously,** as reflected by a catheter-mounted intrarectal pressure balloon, a vaginal catheter, or a catheter inserted next to the bladder. It is true that an experienced operator can very often tell the difference between a true detrusor contraction and an increase in bladder pressure caused by an increase in IAP by the configuration of the curve and by observation of the patient. However, if there is any question about this or if a significant decision is to be based on these data, electronic subtraction of the IAP from the total bladder pressure (yielding detrusor pressure) is desirable.

The normal adult cystometrogram can be divided into four phases (Figure 14-5).

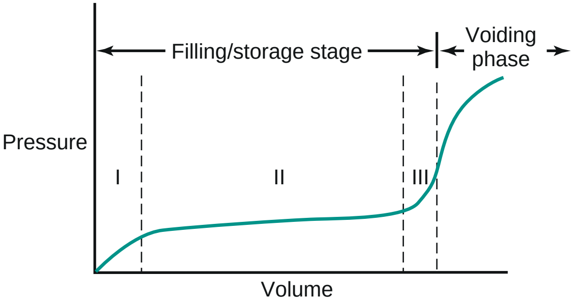

**FIGURE 14-5 Idealized normal adult cystometrogram.** (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

a. **Phase 1:** The initial pressure rise represents the initial response to filling, and the level at which the bladder trace stabilizes is known as the *initial filling pressure*. The first phase of the curve is contributed to by the initial myogenic response to filling and by the elastic and viscoelastic response of the bladder wall to stretch, factors previously discussed. With liquid infusion, the initial filling pressure usually develops gradually and levels off between 0 and 8 cm of water in the supine position. With more rapid rates of filling, there may be an initially higher peak, which then levels off. This peak type of initial response is relatively common with gas cystometry (rarely used). Although this is a detrusor response, its significance is not the same as that of an involuntary bladder contraction during phase 2.
b. **Phase 2:** This is called the **tonus limb**, and **compliance** (**Δ volume/Δ pressure**) **is normally high and uninterrupted by phasic rises.** In practice, the compliance seen in the urodynamic laboratory is always lower than that existing during physiologic bladder filling. It must be remembered that in a normal individual, if the filling rate with liquid is 2.4 times or less than the hourly diuresis rate, phase 2 will be perfectly flat (Bjorn Klemark). Normally, in the urodynamic laboratory, the rise is less than 6 to 10 cm of water. It is difficult to find stated values for normal compliance.
c. **Phase 3:** This is reached when the elastic and viscoelastic properties of the bladder wall have reached their limit. Any further increase in volume generates a substantial increase in pressure. This increase in pressure is not the same as a

detrusor contraction. If a voluntary or involuntary contraction occurs, phase 3 can be obscured by the rise in pressure so generated.

d. **Phase 4:** Ideally, involuntary bladder contractions do not occur during either phase 2 or 3; phase 4 consists of the initiation of voluntary micturition. Many patients are unable to generate a voluntary detrusor contraction in the testing situation, especially in the supine position. This should not be called detrusor areflexia but simply absence of a detrusor contraction during cystometry, a finding that is not considered abnormal unless other clinical or urodynamic findings are present that substantiate the presence of neurologic or myogenic disease.

 **Involuntary bladder contractions** (**DO**) **during filling are always significant.** *Detrusor hyperreflexia* and *detrusor instability* are both terms no longer in use but previously defined by the ICS to relate to the generic term *involuntary bladder contraction*. ***Neurogenic DO*** (**previously *detrusor hyperreflexia***) refers to an involuntary contraction that is the result of associated neurologic disease; ***idiopathic DO*** (**previously *detrusor instability***) refers to an involuntary contraction seen in the absence of neurologic disease. A number of representative adult filling cystometrograms (liquid) are diagrammed in Figure 14-6.

One of the most important urodynamic concepts to remember is that **adequate storage at low intravesical pressure will avoid deleterious upper urinary tract changes in patients with BOO and/or neuromuscular LUT dysfunction.** Ed McGuire and coworkers clearly showed that **upper tract deterioration is apt to occur when storage, even though adequate in terms of continence, occurs at sustained urodynamically generated detrusor pressures higher than 40 cm of water.** Application of this concept to patients with storage problems and specifically those with decreased compliance and incontinence has resulted in the concept of the **detrusor leak point pressure** (**DLPP**) as a very significant piece of urodynamic data. This is to be distinguished from the VLPP described subsequently.

The **DLPP** is also known as the *bladder leak point pressure (BLPP)*. It is important to understand the context in which this test was originally described and the astute intuitive reasoning that went into describing the original concept.

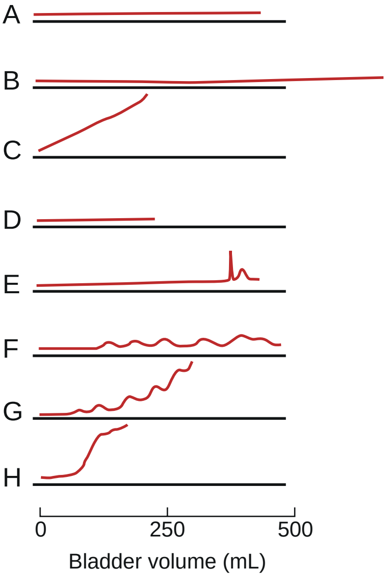

FIGURE 14-6 Various representative adult filling cystometrograms. **A,** Normal filling curve in a patient with a bladder capacity of 450 mL, normal compliance, and no involuntary bladder contractions. Nothing can be said about bladder activity during the emptying phase of micturition from this tracing. **B,** Large-capacity bladder with increased compliance at medium fill rate. This type of curve is characteristic of an individual with decreased sensation and bladder decompensation. Although most individuals will in fact have no or poor detrusor contraction, that conclusion cannot be made on the basis of this curve. **C,** Decreased compliance. **D,** Small-capacity bladder secondary to hypersensitivity without decreased compliance or involuntary bladder contraction. **E,** Bladder contraction provoked by cough. This particular tracing represents total bladder pressure. To make this diagnosis from this tracing alone, the clinician would need to be either a very astute examiner or review separate recordings of intravesical pressure and intraabdominal pressure (IAP) (intrarectal pressure). **F,** Low-amplitude detrusor contraction. This is a subtracted bladder pressure, and this type of recording may be seen most characteristically in a patient with suprasacral neurologic disease or idiopathic detrusor overactivity (DO). **G,** Decreased compliance and involuntary bladder contractions. **H,** High-amplitude early involuntary bladder contraction. (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

In the early 1980s, McGuire and associates studied a group of myelodysplastic children with decreased compliance and incontinence. Those children who did not leak on filling cystometry until their detrusor pressures exceeded 40 cm of water exhibited upper urinary tract deterioration on subsequent follow-up. Classically, the test was performed by passively filling the bladder through a small-caliber urethral catheter with the patient at rest throughout the study, not attempting to volitionally void. The point at which leakage occurs around the catheter is measured as the DLPP. **If the DLPP in such an individual with decreased compliance and incontinence is greater than 40 cm of water, the patient is believed to be at risk for upper tract deterioration.** Thus this test has become extremely useful in the management of such patients with neurogenic bladder dysfunction. An abnormal test dictates the necessity of reducing storage pressure to a point below which upper tract deterioration will subsequently be seen, even if this means combining measures to decrease bladder contractility and increase bladder capacity with intermittent catheterization. **The concept has been extended to cover patients who have decreased compliance and who do not have incontinence, but whose measured detrusor pressure at bladder volumes they often "carry" exceeds 40 cm of water.** Some apply the concept also to patients with involuntary bladder contractions whose detrusor pressures exceed 40 cm of water. Whether this concept truly applies to this latter group of patients, except in instances where this occurs extremely frequently, or where the pressure is maintained once contraction has occurred, is unknown.

As a corollary, **in patients with decreased compliance and incontinence, one must remember that to accurately measure compliance urodynamically, the bladder outlet must be competent or occluded.** This is especially important if there is a plan to correct outlet-related incontinence in an individual with neuromuscular dysfunction associated with decreased compliance (e.g., in the myelomeningocele patient). In other words, one may get a falsely reassuring sense of normal or only slightly decreased compliance in an individual with significant sphincteric insufficiency. Before correcting the sphincteric insufficiency, there needs to be an accurate idea of what bladder compliance will be when the outlet no longer leaks during filling and storage. This can be accomplished very simply by pulling a Foley balloon against the bladder outlet to occlude it during filling.

Cholinergic supersensitivity can be determined during cystometry (**bethanechol supersensitivity test**). This test is based on Cannon's law of denervation, which implies that when an organ is deprived of its nerve supply, it develops hypersensitivity to a variety of substances, including those that are normally excitatory neurotransmitters for that organ. Originally devised by Jack Lapides and associates, the test has remained virtually unaltered since 1962. It involves controlled liquid cystometry at an infusion rate of 1 mL/sec to a volume of 100 mL, when the bladder pressure is measured. After two or three such infusions, an average value is obtained, and this maneuver is repeated 10, 20, and 30 minutes after subcutaneous injection of 2.5 mg or 0.035 mg/kg of bethanechol chloride. A normal bladder shows a response of less than 15 cm of water pressure above the control value at the 100 mL volume. Under these circumstances, a positive result strongly suggests an interruption in the peripheral neural and/or distal spinal pathways to and from the bladder. The more distal and complete the lesion, the more frequently positive the test seems to be. A negative result in an individual with a normal bladder capacity and no detrusor decompensation (admittedly sometimes hard to judge) and in whom the bethanechol is administered on a weight basis, strongly suggests that there is no such lesion. Known factors that can give a falsely positive test include urinary tract infection (UTI), azotemia, detrusor hypertrophy, and emotional stress. A falsely negative study may result from a decompensated bladder that cannot respond to cholinergic stimulation under any circumstances. False-negative results may also be due to an insufficient dose of the cholinergic agonist in a very heavy person, and it is useful to administer bethanechol on a weight basis (0.035 mg/kg) to obviate this. The test is not very useful in individuals with involuntary bladder contractions. Under such circumstances, the cholinergic agonist often simply raises bladder pressure sufficiently to make the involuntary contraction occur at a lower volume than usual. It has never been clear whether this was originally intended to be interpreted as a positive test. If one administers the bethanechol on a weight basis and infection, detrusor hypertrophy, stress, and azotemia have been excluded, there should be few false-positive results.

The **ice water test** was originally described by Bors and Blinn in 1957. Methodology differs among practitioners, but the gist is this: Sterile 0-degree to 4-degree C water or saline is rapidly instilled into the bladder (100 mL within 20 seconds or 200 mL/min to a volume of 30% to 50% of a previously determined cystometric capacity). A positive result is considered a detrusor contraction greater than 30 cm of water, with leakage around the catheter, expulsion of the catheter, or emptying immediately after removal of the catheter. The test has been described as a method of demonstrating a segmental reflex that is inhibited centrally in healthy adult subjects without neurologic lesions but which appears when suprasacral lesions are present, but normally occurs in infants and young children. The afferent fibers for the ice water test are thought to be unmyelinated C-fiber afferents, which are normally silent during filling and storage but which become functional with various types of neurologic disease or injury. Thus, a positive test can be considered indicative of a neurologic lesion, even though the neurologic lesion may not become manifest until a subsequent time. However, everyone with such a lesion may not have a positive ice water test.

5. **Voiding cystometry, combined pressure studies, and video urodynamic studies**

Intravesical pressure, IAP (generally reflected by intrarectal pressure), and flow are often measured simultaneously (Figure 14-7). The purposes of pressure/flow urodynamic studies (**PFUDS**) are to be able to better define whether obstruction is present and to assess detrusor contractility more precisely. By assessing patterns of detrusor pressure and flow, thereby inferring resistance and patterns of increased resistance, the examiner can often ascertain the exact pathology (e.g., anatomic obstruction versus dyssynergia). **The normal adult male generally voids with a detrusor pressure of between 40 and 50 cm of water.**

The **normal adult female voids at a much lower pressure.** Indeed, many women void with almost no detectable rise in detrusor pressure. This does not indicate that contraction is not occurring but simply that outlet resistance, lower in the female to begin with, drops to very low levels during bladder contraction. It should be remembered, however, as Derek

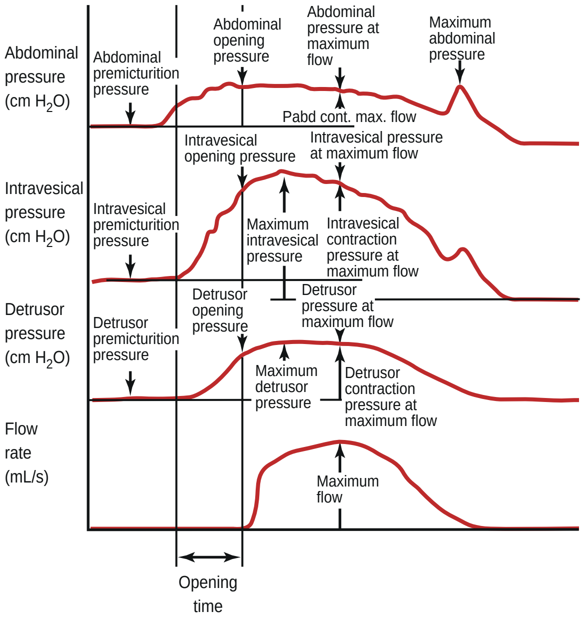

**FIGURE 14-7 Recommended International Continence Society (ICS) registration of combined pressure(s) and flow recording.** (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

Griffiths, a pioneer urodynamicist, has pointed out, that detrusor pressure alone is insufficient to assess the strength of a detrusor contraction. This is because a muscle can use energy to either generate force or shorten its length. With respect to the bladder, a relatively hollow viscus, the force developed contributes to detrusor pressure whereas the velocity of shortening contributes to flow. With significant obstruction, detrusor pressure can rise to high levels. If resistance is very low, detrusor pressure may be undetectable but the contractility may be equal in the two instances.

**Urodynamically, obstruction is generally defined only by the relationship between detrusor pressure and flow (i.e., high pressure and low flow).** Pressure flow studies can be analyzed according to a number of nomograms, a detailed description of which is beyond the scope of this chapter. We find that most often, a detailed visual analysis of the entire study is just as or more helpful. **Two easy and useful concepts to remember in this regard are the Abrams-Griffiths (AG) number or bladder outlet obstruction index (B00I), and the bladder contractility index (BCI).** The B00I relates to whether outlet obstruction is present in the male. It is calculated as [Pdet @ $Q_{max}$ – $2Q_{max}$]. A value greater than 40 indicates obstruction, less than 20 indicates no obstruction, and 20 to 40 is considered equivocal. The BCI is calculated as [Pdet @ $Q_{max} + 5Q_{max}$]. Over 150 indicates a "strong" bladder, 100 to 150 a normal one, and less than 100 a "weak" bladder. There are many other formulas, integrated numbers, and graphs that are designed to assess flow and detrusor contractibility, strength, and work. There are no universal precepts in this regard at this time. The majority apply to men only.

**Once obstruction is diagnosed, it is necessary to determine the site, and to do this, simultaneous fluoroscopy is often used.** This **VUDS combines the cystourographic imaging described previously with simultaneous urodynamic studies, permitting a generally accurate determination of the site of obstruction at the time high pressure and low flow coexist. VUDS is also extremely useful in assessing the etiology of complex cases of incontinence because the precise pressure relationships existing in the bladder and urethra can be correlated with the cystourethrographic radiologic patterns, and therefore a judgment can be made of why involuntary leakage occurs at a particular time.** In this case, the issue is generally whether the fluoroscopic demonstration of leakage occurs with or without DO or whether the incontinence is due in part to both detrusor and outlet-related causes. VUDS also can demonstrate other bladder pathology (e.g., diverticula, reflux, external compression or displacement, abnormal shape), abnormal activity of the sphincter areas during filling/storage and emptying/voiding, and pathologic descent of the bladder base and proximal urethra.

One of the most difficult problems in urodynamics is the clarification of whether contractile function is adequate, that is, whether it is sustained and coordinated. **Phasic DO does not imply normal contractile function. There is a subset of patients with incontinence in whom DO and impaired contractile function coexist** — so-called *detrusor hyperactivity* *with impaired contractility (DHIC)*. The detrusor is overactive in these patients during filling/storage, but empties ineffectively because of diminished detrusor contractile function and not necessarily because of outlet obstruction. In some patients, obstruction coexists with impaired detrusor contractility, and this diagnosis often cannot be made. Several very sophisticated resistance formulas exist that attempt to calculate a number for outlet resistance, utilizing data based on intravesical pressure, flow rate, and other mathematical factors. These formulas generally assume that the urethra is a rigid tube with a constant diameter and that the pressure always reflects that generated by a normal bladder, not a decompensated one. If a bladder has normal contractility and the pressure that it generates during contraction is high and if the corresponding flow rate that results is low, one does not need a formula to diagnose obstruction. On the other hand, if the bladder is decompensated and incapable of producing a significant rise in pressure, obstruction cannot be quantitated by these formulas. More sophisticated and innovative methods of defining the relationship between intravesical pressure and uroflow have been devised, and the worth of these methods and debates are beyond the scope of this discussion of urodynamics. The global question surrounding all noncomputer-assisted and computer-assisted characterizations and interpretations of pressure flow data is: What do these add? Is the evaluation of the average older man with LUT symptoms more likely to lead to a better treatment outcome if PFUDS or VUDS is performed, including the analysis of results in various mathematical ways with computer assistance? Do sophisticated or unsophisticated urodynamic studies predict the outcome of various treatments for LUTS, including watchful waiting? Are patients with LUTS in whom outlet ablation fails as treatment the same patients as those in whom detrusor contractility is judged ineffective by the criteria under consideration? Unfortunately, those of us who perform urodynamics have not done a terribly good job of looking into these aspects of outcome analysis. Figure 14-7 displays the ICS's recommended registration of combined pressure and flow recording. Kinesiologic electromyography is often added as an additional channel, and some investigators record urethral pressure at one or various sites along the urethra simultaneously as well. The typical VUDS configuration includes this and a fluoroscopic lower tract image.

6. **Electromyography**

   For the majority of urologists, electromyography is a urodynamic study that permits evaluation of the striated sphincter during the emptying phase of micturition. ***Kinesiologic electromyography*** is the term that describes this application, that is, the study of the activity of one group of muscles (the striated musculature of the outlet) with respect to another (the bladder). **Normally, as the bladder fills with urine, there is a gradual and sustained increase in electromyographic (EMG) activity recruited from the pelvic floor muscles. This reaches a maximum just before voiding.** Compositely, this is known as the ***guarding reflex***. The lack of a guarding reflex suggests neural pathology, as does the inability to produce a sphincter "flare" when given the command to "stop voiding." **Voluntary voiding is normally followed by complete electrical silence-relaxation of the striated sphincter**. There is a marked increase in EMG activity in response to a number of stimuli, including cough, Credé and Valsalva maneuvers, the BCR, and the request to stop voiding, a maneuver accomplished by most through forceful contraction of the pelvic floor musculature (Figure 14-8). Kinesiologic electromyography enables the urodynamic examiner to ascertain whether the striated sphincter appropriately increases its activity in a gradual fashion during bladder filling (whether the guarding reflex is normal) and whether quiescence occurs normally before and during bladder contraction. Kinesiologic electromyography can be performed with either needle electrodes or surface or patch electrodes. Needle electrodes certainly permit more accurate placement and more accurate recording, but in many cases, surface electrodes seem perfectly adequate to obtain the necessary information. **When EMG activity gradually increases during filling cystometry and then ceases prior to or at the onset of attempted voiding, this is normal and can be taken as a reflection of what goes on during actual bladder filling and emptying.** However, **a simultaneous increase of EMG activity with an increase in intravesical pressure during filling cystometry is not always indicative of detrusor-striated**

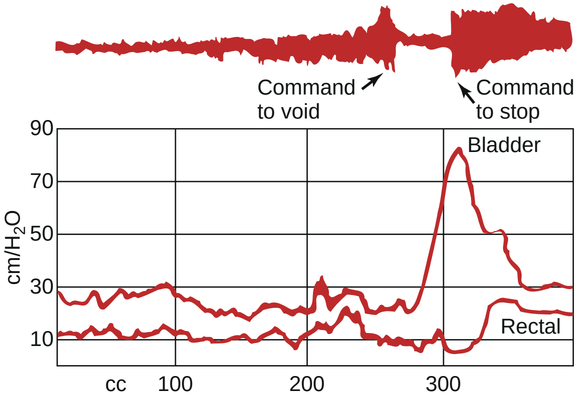

FIGURE 14-8 Normal pressure electromyographic tracing. Note the gradual increase in electromyographic activity during bladder filling (this is called the guarding reflex) with a decrease to control levels just before the onset of what is voluntary bladder contraction. Note that the command to stop voiding evokes a pelvic-floor striated muscle contraction reflected by a flare in sphincter electromyography. (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

**sphincter dyssynergia. Abdominal straining or attempted inhibition of a bladder contraction will yield an identical pattern.** For a patient with normal sensation, no matter how cooperative, it is extremely difficult to maintain true relaxation during an involuntary bladder contraction. In fact, the appropriate response is to try to suppress such a contraction by voluntary contraction of the anal sphincter, the pelvic floor musculature, or both. All of these circumstances represent types of **pseudodyssynergia** and are extremely difficult to differentiate from true dyssynergia on the basis of any type of urodynamic study done solely during bladder filling. The term ***detrusor-striated sphincter dyssynergia***, generally referred to as just *detrusor sphincter dyssynergia (DSD)*, should refer to obstruction to the outflow of urine during bladder contraction caused by involuntary contraction of the striated sphincter. This is most often seen in patients with discrete neurologic disease, such as suprasacral spinal cord transection after spinal shock has passed. Individuals suspected of having detrusor-striated sphincter dyssynergia but who lack identifiable neurologic disease should always be further investigated with sophisticated video urodynamic evaluation during a full micturition study. True detrusor-striated sphincter dyssynergia is extremely uncommon (some examiners say that it does not exist) in patients without neurologic disease, and such a diagnosis deserves exhaustive study before it is in fact confirmed.

7. **Urethral profilometry**

   The term *urethral profilometry* refers to many entities utilized in various settings. The most common usage refers to a **static infusion urethral pressure profile.** In this study, a small catheter with radially drilled side holes is placed in the bladder and through it a medium, usually liquid, is infused. The catheter is then withdrawn at a constant rate, and the pressure required to push the medium through the side holes is recorded from inside the bladder to a site where the pressure becomes essentially isobaric with bladder pressure. The infusion profile curve is thus a result of a number of factors, including urethral wall compliance, resistance to inflow of the medium, resistance to runoff of the medium into the bladder and out the urethral meatus, and artifact generated by the apparatus. Because the study is usually done at rest and not during bladder filling or emptying, it is difficult to associate the recorded events with bladder-urethral interaction during filling or emptying. Specifically with relevance to neuromuscular dysfunction, the static infusion profile has been cited as useful at various times in history in diagnosing stress incontinence, DSD, and obstruction. In our opinion, it is not very useful for the specific diagnosis of any of these. There is much overlap in maximum urethral pressures and functional urethral lengths between individuals with stress incontinence and normal individuals, especially in the elderly population. The rationale of diagnosing either smooth or striated sphincter dyssynergia on the basis of a static infusion profile is difficult to understand. A high pressure at a given point in the passage of the catheter from the bladder through the urethra can be secondary to a number of phenomena, and this result by no means indicates that there will always be contraction or obstruction in this area during voluntary or involuntary micturition. The static infusion urethral profile is certainly useful for testing the function of an artificial genitourinary sphincter. With specific relevance to neuromuscular dysfunction, it is useful for suspecting intrinsic sphincter dysfunction. In an individual with such an abnormality (Figures 14-9 and 14-10), the proximal urethra is isobaric or almost isobaric with the bladder, and the striated sphincter peak is generally lower than normal.

**Stress urethral profilometry** refers to a study done with a catheter with dual sensors, one in the bladder and one in the proximal urethra. With coughing or straining, the change in urethral pressure should always be equal to or greater than the change in bladder pressure. In patients with stress incontinence, along with much of the profile curve, the change in urethral pressure will be less than the change in bladder pressure. **Dynamic urethral profilometry** implies the use of a catheter with dual sensors — bladder and proximal urethra — with pressures recorded during bladder filling and emptying. An actual urethral pressure profile is not recorded. The interaction between bladder pressure and pressure in one area of the

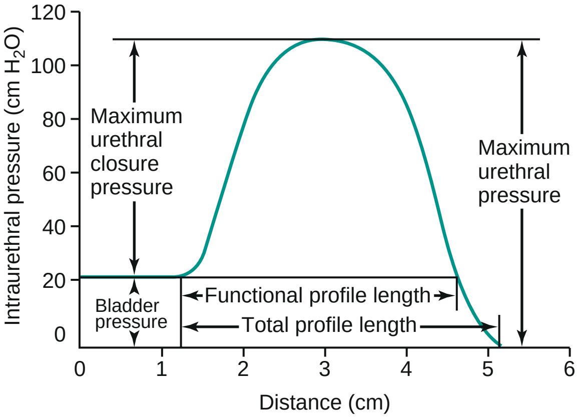

**FIGURE 14-9 Idealized static infusion urethral pressure profile utilizing International Continence Society (ICS) nomenclature (female).** (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

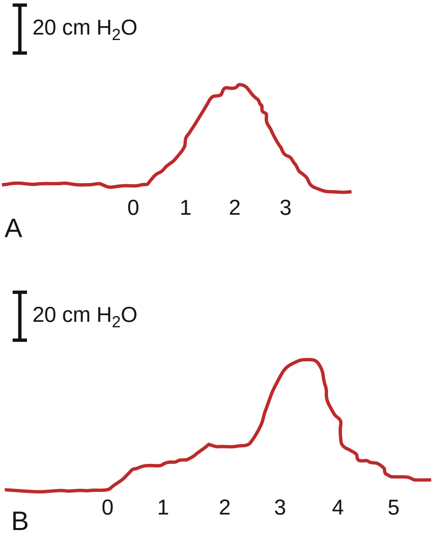

FIGURE 14-10 Actual static infusion urethral pressure profiles from normal female **(A)** and male **(B)** subjects. Numbers represent centimeters with 0 representing the level of the bladder neck. The maximum urethral pressure in both males and females is normally at the level of the urogenital diaphragm. The initial portion of the curve in the male, from the bladder neck to the pressure rise culminating at the maximum urethral pressure, is sometimes called *prostatic plateau*. The area under this portion of the curve corresponds roughly to prostatic size. (From Wein AJ, English WS, Whitmore KE: Office urodynamics, *Urol Clin North Am* 15:609–623, 1988.)

urethra, generally in the area of maximal closure pressure, usually at the level of the striated sphincter, is recorded.

**Micturitional urethral profilometry** refers to a study in which a catheter with dual or triple sensors, one of which is in the bladder, is withdrawn during voiding in a patient with known obstruction. In such a patient, the area of the maximal pressure drop is the site of obstruction. Micturitional profilometry generally requires fluoroscopic monitoring to identify the anatomic location of this maximal pressure decrease.

8. **Abdominal leak point pressure**

The abdominal leak point pressure (ALPP) is a measure of the ability of the urethra to resist changes in abdominal pressure as an expulsive force. It has been popularized by Ed McGuire as a clinically useful test, perhaps the most useful one to differentiate the extremes of ISD from hypermobility-related stress incontinence. It is easy to see why the concept of this test appeals to straightforward logic: **If straining or increases in IAP produce incontinence, and a filling study shows normal compliance, there must be a problem with the bladder outlet. The amount of abdominal pressure necessary to cause leakage under such circumstances is inversely proportional to the amount of outlet dysfunction**. A pressure catheter is placed in the bladder or rectum or both, and the bladder is filled to a predetermined volume, usually 150 to 200 mL. The patient is then asked to perform a graded Valsalva maneuver until leakage is seen per urethra. If this does not produce leakage, the patient is asked to cough. The pressure at which leakage is first seen is the ALPP. The higher the ALPP, the better the intrinsic sphincter function, and, conversely, the lower the ALPP, the worse the intrinsic sphincter function.

There are still problems concerning standardization of technique, specification of variables, optimal location of pressure measurement, size of urethral catheter to be used, and the bladder volume at which the study is to be carried out. There is also disagreement about what “numbers” indicate a significant degree of intrinsic sphincter dysfunction. Originally, an ALPP of less than 60 to 65 cm of water was said to indicate ISD. One caveat to remember is that a large cystocele can invalidate the results, making the ALPP artificially higher.

9. **Ambulatory urodynamics**

An obvious limitation to routine or conventional urodynamic testing is the artificial environment and circumstances in which the test is conducted. Ambulatory urodynamics is an alternative technique in which the pressure-transducing catheters are placed into the bladder and rectum but are attached to portable recording devices. The patient resumes his or her normal daily routine and cycles of natural bladder filling and storage. Emptying and voiding are recorded, while the patient writes down the time and qualitative nature of relevant subjective sensations. Provocative maneuvers such as coughing, climbing, jumping, and hand washing can be performed in an attempt to reproduce the patient’s symptomatology. At the conclusion of the study, the data are downloaded to a computer, compared with the written record of symptomatology, and analyzed. **Advocates of this type of study cite the ability to objectively confirm the complaints of many patients in whom nonambulatory urodynamics have been unrevealing.** However, **limitations of this study include the following:** (1) the triggering effect of a catheter in the bladder can cause a higher incidence of involuntary bladder contractions than in standard cystometry; (2) if one is recording urethral pressures as well, small movements of the catheter are unavoidable in an ambulatory patient, often resulting in artificial pressure dips; (3) measurement of actual leakage is difficult or near impossible; (4) the bladder-filling rate depends on many factors that are still not controllable (such as intake, diuretic usage, and congestive failure); (5) different states of rectal filling and rectal catheter stimulation in the ambulatory patient may exert reflex effects on the bladder; (6) it is difficult to simultaneously measure flow during ambulatory urodynamics, and so at present the study is more useful in the evaluation of filling and storage abnormalities than emptying/voiding abnormalities; (7) detrusor pressure values for certain parameters are different during ambulatory urodynamics as opposed to laboratory urodynamics (new agreed-on standards for normality and abnormality need to be developed); and (8) a certain percent of records will be unable to be interpreted because of artifacts. At present, ambulatory urodynamics are utilized primarily as a research tool, although the potential range of clinical applications, with some technologic improvements, are numerous.

## Classification of LUT Dysfunction

### GENERAL

There are many classification systems for LUT dysfunction, and these are based on neurologic, urodynamic, or functional considerations, or on a combination of these. That there are at least six to eight of these attests to the fact that none is prefect. The **purpose of any classification system** should be to facilitate understanding and management and to avoid confusion among those who are concerned with the problem for which the system was designed. A good classification should serve as intellectual shorthand and should convey, in a few key words or phrases, the essence of a clinical situation. Most systems of classification for LUT dysfunction were formulated primarily to describe dysfunction secondary to neurologic disease or injury. The ideal system should be applicable to all types of LUT dysfunction.

In this section, we describe the functional type of classification that we have found most useful and also the International Continence Society classification and the Lapides system. A more exhaustive listing can be found in *Campbell-Walsh Urology*.

## THE FUNCTIONAL SYSTEM

Classification of LUT dysfunction can be formulated on a simple functional basis, describing the dysfunction in terms of whether the deficit produced is primarily one of the filling/storage or the emptying/voiding phase of micturition (see Tables 14-3 and 14-4). The genesis of such a system was proposed initially by F. Brantley Scott's group. This simple-minded scheme assumes only that, whatever their differences, "experts" would agree on the two-phase concept of micturition (filling/storage and emptying/voiding) and on the simple overall mechanisms underlying the normality of each phase.

**Storage failure** results because of either **bladder or outlet abnormalities or a combination.** The proven **bladder abnormalities** very simply include only involuntary bladder contractions, low compliance, and heightened or altered sensation. The **outlet abnormalities** can include only an intermittent or continuous decrease in outlet resistance.

**Emptying failure,** likewise, can occur because of **bladder or outlet abnormalities or a combination.** The **bladder side** includes only inadequate, uncoordinated, or unsustained bladder contractility, and the **outlet side** includes only anatomic obstruction and sphincter(s) dyssynergia (functional obstructions).

Failure in either category generally is not absolute, but more often is relative. **There are indeed some types of LUT dysfunction that represent combinations of filling/storage and emptying/voiding abnormalities.** Within this scheme, however, these become readily understandable and their detection and treatment can be logically described. Various aspects of physiology and pathophysiology are always related more to one phase of micturition than another. All aspects of urodynamic and video urodynamic evaluation can be conceptualized in this functional manner as to exactly what they evaluate in terms of either bladder or outlet activity during filling/storage and emptying/voiding (see Table 14-6). In addition, one can easily classify all known treatments for LUT dysfunction under the broad categories of whether they facilitate filling/storage and emptying/voiding and whether they do so by an action primarily on the bladder or on one or more of the components of the bladder outlet (Tables 14-7 and 14-8).

TABLE 14-7 **Therapy to Facilitate Urine Storage/Bladder Filling**

I. Bladder related (inhibiting bladder contractility, decreasing sensory input, and/or increasing bladder capacity)
    A. Behavioral therapy, including any or all of:
        1. Education
        2. Bladder training
        3. Timed bladder emptying or prompted voiding
        4. Fluid restriction
        5. Pelvic floor physiotherapy ± biofeedback
    B. Pharmacologic therapy (oral, intravesical, intradetrusor)
        1. Antimuscarinic agents
        2. Beta-adrenergic agonists
        3. Botulinum toxin
        4. Drugs with mixed actions
        5. Calcium antagonists
        6. Potassium channel openers
        7. Prostaglandin inhibitors
        8. Alpha-adrenergic antagonists
        9. Tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitors
        10. Dimethyl sulfoxide (DMSO)
        11. Polysynaptic inhibitors
        12. Capsaicin, resiniferatoxin, and similar agents
    C. Bladder overdistention
    D. Electrical stimulation (sacral neuromodulation, posterior tibial and other peripheral nerve stimulation)
    E. Acupuncture and electroacupuncture
    F. Interruption of innervation
        1. Very central (subarachnoid block)
        2. Less central (sacral rhizotomy, selective sacral rhizotomy)
        3. Peripheral motor or/and sensory
    G. Augmentation cystoplasty (auto, bowel, tissue engineering)

(*Continued*)

TABLE 14-7 **Therapy to Facilitate Urine Storage/Bladder Filling—Cont'd**

- II. Outlet related (increasing outlet resistance)
    - A. Behavioral therapy, including any or all of:
        - 1. Education
        - 2. Bladder training
        - 3. Timed bladder emptying or prompted voiding
        - 4. Fluid restriction
        - 5. Pelvic floor muscle training ± biofeedback
    - B. Electrical stimulation
    - C. Pharmacologic therapy
        - 1. Alpha-adrenergic agonists
        - 2. Tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitors
        - 3. Beta-adrenergic antagonists, agonists
    - D. Vaginal and perineal occlusive and/or supportive devices; urethral plugs
    - E. Nonsurgical periurethral bulking
        - 1. Synthetic bulking agents, tissue engineering
    - F. Retropubic vesicourethral suspension ± prolapse repair (female)
    - G. Sling procedures ± prolapse repair (female)
    - H. Midurethral tapes ± prolapse repair (female)
    - I. Perineal sling procedure (male)
    - J. Artificial urinary sphincter
    - K. Myoplasty (muscle transposition)
    - L. Bladder outlet closure
- III. Circumventing the problem
    - A. Absorbent products
    - B. External collecting devices
    - C. Antidiuretic hormonelike agents
    - D. Short-acting diuretics
    - E. Intermittent catheterization
    - F. Continuous catheterization
    - G. Urinary diversion

**Such a functional system can easily be "expanded" and made more complicated to include etiologic or specific urodynamic connotations** (see Table 14-4). However, the simplified system is perfectly workable and avoids argument in those complex situations in which the exact etiology or urodynamic mechanism for a voiding dysfunction cannot be agreed on.

TABLE 14-8 **Therapy to Facilitate Bladder Emptying/Voiding**

- I. Bladder related (increasing intravesical pressure or facilitating bladder contractility)
  - A. External compression, Valsalva
  - B. Promotion or initiation of reflex contraction
    - 1. Trigger zones or maneuvers
    - 2. Bladder “training,” tidal drainage
  - C. Pharmacologic therapy (oral, intravesical)
    - 1. Parasympathomimetic agents
    - 2. Prostaglandins
    - 3. Blockers of inhibition
      - a. Alpha-adrenergic antagonists
      - b. Opioid antagonists
  - D. Electrical stimulation
    - 1. Directly to the bladder or spinal cord
    - 2. Directly to the nerve roots
    - 3. Intravesical (transurethral)
    - 4. Sacral neuromodulation
  - E. Reduction cystoplasty
  - F. Bladder myoplasty (muscle wrap)
- II. Outlet related (decreasing outlet resistance)
  - A. At a site of anatomic obstruction
    - 1. Pharmacologic therapy — decrease prostate size or tone
      - a. Alpha-adrenergic antagonists
      - b. 5-alpha-reductase inhibitors
      - c. Luteinizing hormone-releasing hormone agonists/antagonists
      - d. Antiandrogens
    - 2. Prostatectomy, prostatotomy (diathermy, heat, laser)
    - 3. Bladder neck incision or resection
    - 4. Urethral stricture repair or dilation
    - 5. Intraurethral stent
    - 6. Balloon dilation of stricture/contracture
  - B. At level of smooth sphincter
    - 1. Pharmacologic therapy
      - a. Alpha-adrenergic antagonists
    - 2. Transurethral resection or incision
    - 3. Y-V plasty

(*Continued*)

TABLE 14-8 **Therapy to Facilitate Bladder Emptying/Voiding—Cont'd**

- C. At level of striated sphincter
    - 1. Behavioral therapy ± biofeedback
    - 2. Pharmacologic therapy
        - a. Benzodiazepines
        - b. Baclofen
        - c. Dantrolene
        - d. Alpha-adrenergic antagonists
        - e. Botulinum toxin (injection)
    - 3. Urethral overdilation
    - 4. Surgical sphincterotomy
    - 5. Urethral stent
    - 6. Pudendal nerve interruption
- III. Circumventing the problem
    - A. Intermittent catheterization
    - B. Continuous catheterization
    - C. Urinary diversion (conduit or reservoir)

Proper use of the functional system for a given LUT dysfunction obviously requires a reasonably accurate notion of what the urodynamic data show. However, **an exact diagnosis is *not* required for treatment.** It should be recognized that **some patients do not have only a discrete storage or emptying failure, and the existence of combination deficits must be recognized to properly utilize this system of classification.** For instance, the classic T10 paraplegic patient after spinal shock generally exhibits a relative failure to store because of involuntary bladder contraction and a relative failure to empty the bladder because of striated sphincter dyssynergia. With such a combination deficit, to utilize this classification system as a guide to treatment, one must assume that one of the deficits is primary and that significant improvement will result from its treatment alone or that the LUT dysfunction can be converted primarily to a disorder of either storage or emptying by means of nonsurgical or surgical therapy. The resultant deficit can then be treated or circumvented. Using this example, the combined deficit in a T10 paraplegic patient can be converted primarily to a storage failure by procedures directed at the dyssynergic striated sphincter; the resultant incontinence (secondary to involuntary contractions) can be circumvented (in a male) with an external collecting device. Alternatively, the deficit can be converted primarily to an emptying failure by pharmacologic or surgical measures designed to abolish or reduce the involuntary contractions, and the resultant emptying failure can then be circumvented with clean intermittent catheterization (CIC). Other examples of combination deficits include impaired bladder contractility or overactivity with sphincter dysfunction, BOO with DO, BOO with sphincter malfunction, DO during filling/storage with impaired contractility during emptying, and sphincteric incontinence with DO or impaired bladder contractibility.

One of the advantages of this functional classification is that it allows the clinician the liberty of "playing" with the system to suit his or her own preferences without an alteration in the basic concept of "keep it simple but accurate and informative." For instance, one could easily substitute the terms *overactive or oversensitive bladder* and *underactive outlet* for *because of the bladder* and *because of the outlet* under "Failure to store" in Table 14-3. One could choose to categorize the bladder reasons for overactivity (see Table 14-4) further in terms of neurogenic, myogenic, or anatomic causes and further subcategorize neurogenic in terms of decreased inhibitory control, increased afferent activity, increased sensitivity to efferent activity, and so on. The system is flexible and it works.

## INTERNATIONAL CONTINENCE SOCIETY CLASSIFICATION

The classification system proposed by the ICS (Table 14-9) is in **essence an extension of a urodynamic classification system.** The storage and voiding phases of micturition are described separately, and, within each, various designations are applied to describe bladder and urethral function. Some of the definitions were changed by the standardization subcommittee of the ICS in 2002 and the relevant changes are indicated here. **Normal bladder function during filling/storage implies no significant rises in detrusor pressure (stability). Overactive detrusor function indicates the presence of "involuntary detrusor contractions during the filling phase which may be spontaneous or provoked."** If caused by neurologic disease, the term ***neurogenic DO*** (previously *detrusor hyperreflexia*) is used; if not, the term ***idiopathic DO*** (previously *detrusor instability*) is applied. **Bladder sensation** can be categorized only in qualitative terms as indicated. **Bladder capacity and compliance** (Δ volume/Δ pressure) are cystometric measurements.

TABLE 14-9 **International Continence Society Classification**

| Storage Phase | Voiding Phase |
|---|---|
| **Bladder function** | **Bladder function** |
| Detrusor activity | Detrusor activity |
| Normal or stable | Normal |
| Overactive | Underactive |
| Neurogenic | Acontractile |
| Idiopathic | Areflexic |
| Bladder sensation | |
| Normal | **Urethral function** |
| Increased or hypersensitive | Normal |
| Reduced or hyposensitive | Abnormal |
| Absent | Mechanical obstruction |
| Bladder capacity | Overactivity |
| Normal | Dysfunctional voiding |
| High | Detrusor sphincter dyssynergia (DSD) |
| Low | |
| | Nonrelaxing urethral sphincter dysfunction |
| **Urethral function** | |
| Normal closure mechanism | |
| Incompetent closure mechanism | |

Bladder capacity can refer to cystometric capacity, maximum cystometric capacity, or maximum anesthetic cystometric capacity. **Normal urethral function during filling/storage indicates a positive urethral closure pressure (urethral pressure minus bladder pressure) even with increases in IAP, although it may be overcome by DO. Incompetent urethral function during filling/storage** implies urine leakage in the absence of a detrusor contraction. This may be secondary to classical stress incontinence, intrinsic sphincter dysfunction, a combination, or an involuntary fall in urethral pressure in the absence of detrusor contraction.

**During the voiding/emptying phase of micturition, normal detrusor activity** implies voiding by a voluntarily initiated sustained contraction that leads to complete bladder emptying within a normal time span. An **underactive detrusor** defines a contraction of inadequate magnitude and/or duration to empty the bladder within a normal time span. An **acontractile detrusor** is one that cannot be demonstrated to contract during urodynamic testing.

**Areflexia** is defined as acontractility due to an abnormality of neural control, implying the complete absence of centrally coordinated contraction. **Normal urethral function** during voiding indicates a urethra that opens and is continuously relaxed to allow bladder emptying at a normal pressure. **Abnormal urethra function during voiding may be due to either mechanical obstruction or urethral overactivity. Dysfunctional voiding** describes an intermittent or/and fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle in neurologically normal individuals. **DSD** defines a detrusor contraction concurrent with an involuntary contraction of the urethral or periurethral striated muscle or both. **Nonrelaxing urethral sphincter obstruction** usually occurs in individuals with a neurologic lesion and is characterized by a nonrelaxing obstructing urethra resulting in reduced urine flow.

LUT dysfunction in a classical T10-level paraplegic patient after spinal shock has passed would be classified in the ICS system as follows:

- Storage phase — overactive neurogenic detrusor function, absent sensation, low capacity, normal compliance, normal urethral closure function
- Voiding phase — overactive detrusor function, overactive obstructive urethral function

The micturition dysfunction of a stroke patient with urgency incontinence would most likely be classified during storage as overactive neurogenic detrusor function, normal sensation, low capacity, normal compliance, and normal urethral closure function. During voiding (this refers to voluntary micturition), the dysfunction would be classified as normal detrusor activity and normal urethral function, assuming that no anatomic obstruction existed.

## LAPIDES CLASSIFICATION

Jack Lapides contributed significantly to the classification and care of the patient with neuropathic voiding dysfunction by slightly modifying and popularizing a system originally proposed by McLellan in 1939 (Table 14-10). Lapides classification differs from that of McLellan in only one respect, and that is the division of the group of “atonic neurogenic bladder” into sensory neurogenic and motor neurogenic bladder. This remains one of the most familiar systems to urologists and others because it describes in

TABLE 14-10 **Lapides Classification**

| |
|---|
| Sensory neurogenic bladder |
| Motor paralytic bladder (motor neurogenic bladder) |
| Uninhibited neurogenic bladder |
| Reflex neurogenic bladder |
| Autonomous neurogenic bladder |

recognizable shorthand the clinical and cystometric conditions of many types of neurogenic voiding dysfunction.

A **sensory neurogenic bladder** results from disease that selectively interrupts the sensory fibers between the bladder and the spinal cord or the afferent tracts to the brain. **Diabetes mellitus, tabes dorsalis, and pernicious anemia** are most commonly responsible. The first clinical changes are described as those of impaired sensation of bladder distention. Unless voiding is initiated on a timed basis, varying degrees of bladder overdistention can result with resultant hypotonicity. If bladder decompensation occurs, significant amounts of residual urine result, and at that time, the cystometric curve generally demonstrates a large capacity bladder with a flat, high-compliance, low-pressure filling curve.

A **motor paralytic bladder** results from disease processes that destroy the parasympathetic motor innervation of the bladder. **Extensive pelvic surgery or trauma** may produce this. **Herpes zoster** has been listed as a cause as well, but recent evidence suggests that the voiding dysfunction seen with herpes may be more related to a problem with afferent input. The early symptoms of a motor paralytic bladder may vary from painful urinary retention to only a relative inability to initiate and maintain normal micturition. Early cystometric filling is normal but without a voluntary bladder contraction at capacity. Chronic overdistention and decompensation may occur, resulting in a large-capacity bladder with a flat, low-pressure filling curve; a large residual of urine may result.

An **uninhibited neurogenic bladder** was described originally as resulting from injury or disease to the “corticoregulatory tract.” The sacral spinal cord was presumed to be the micturition reflex center, and the corticoregulatory tract was believed to normally exert an inhibitory influence on the sacral micturition reflex center. A destructive lesion in this tract would then result in overfacilitation of the micturition reflex. **Cerebrovascular**

**accident (CVA), brain or spinal cord tumor, PD, and demyelinating disease** were listed as the most common causes in this category. The LUT dysfunction is most often characterized symptomatically by frequency, urgency, and urge incontinence and urodynamically by normal sensation with involuntary contraction at low filling volumes. Residual urine is characteristically low unless anatomic outlet obstruction or true smooth or striated sphincter dyssynergia occurs. The patient generally can initiate a bladder contraction voluntarily but is often unable to do so during cystometry because sufficient urine storage cannot occur before involuntary contraction is stimulated.

**Reflex neurogenic bladder** describes the postspinal shock condition that exists after complete interruption of the sensory and motor pathways between the sacral spinal cord and the brain stem. Most commonly, this occurs in **traumatic SCI and transverse myelitis,** but it may occur with **extensive demyelinating disease or any process that produces significant spinal cord destruction.** Typically, there is no bladder sensation, and there is inability to initiate voluntary micturition. Incontinence without sensation generally results because of low-volume involuntary contractions. Striated sphincter dyssynergia is the rule.

An **autonomous neurogenic bladder** results from complete motor and sensory separation of the bladder from the sacral spinal cord. This may be caused by any disease that destroys the sacral cord or causes extensive damage to the sacral roots or pelvic nerves. There is inability to voluntarily initiate micturition, no bladder reflex activity, and no specific bladder sensation. This is the type of dysfunction seen in patients with spinal shock. The characteristic cystometric pattern is initially similar to the late stages of the motor or sensory paralytic bladder, with a marked shift to the right of the cystometric filling curve and a large bladder capacity at low intravesical pressure. However, decreased compliance may develop, secondary either to chronic inflammatory change or to the effects of denervation/decentralization with secondary neuromorphologic and neuropharmacologic reorganizational changes. Emptying capacity may vary widely, depending on the ability of the patient to increase intravesical pressure and on the resistance offered during this increase by the smooth and striated sphincters.

These classic categories in their usual settings are generally easily understood and remembered, and this is why this system provides an excellent framework for teaching some fundamentals of neurogenic LUT dysfunction to students and others. Unfortunately, many patients do not exactly "fit" into one or another category. Gradations of sensory, motor, and mixed lesions occur, and the patterns produced after different types of peripheral denervation/decentralization may vary widely from those that are classically described. The **system is applicable only to neuropathic dysfunction.**

## Neurogenic LUT Dysfunction

### GENERAL PATTERNS

Discrete neurologic lesions generally affect the filling/storage and emptying/voiding phases of LUT function in a relatively consistent fashion. **This fashion is dependent on (1) the area(s) of the nervous system affected, and whether the area is completely or incompletely involved (2) the physiologic function(s) and the contents and location of the area(s) affected, and (3) whether the lesion or process is destructive or irritative.** The acute dysfunction produced may differ from the chronic one for a variety of reasons.

Table 14-11 summarizes many of these dysfunctions on the basis of the most common type of abnormal pattern that results from a given disease or injury, insofar as the parameters just listed are concerned. This abbreviated classification is not meant to be all inclusive but to simply indicate that, for the most part, an individual with a specific neurologic abnormality, and LUT dysfunction because of it, will, in general, have the type of dysfunction shown.

1. **Lesions above the brainstem**

   Neurologic lesions above the brainstem that affect micturition generally result in involuntary bladder contractions with coordinated sphincter function (smooth and striated sphincter synergy). Sensation and voluntary striated sphincter function are generally preserved, but sensation may be deficient or delayed. Detrusor areflexia may, however, occur either initially or as a permanent dysfunction. UI may occur due to the DO.

2. **Complete spinal cord lesions above the sacral spinal cord**

   Such patients, after they recover from spinal shock, generally exhibit involuntary bladder contractions without sensation, smooth sphincter synergy, and striated sphincter dyssynergia. Those with lesions above T6 also may

TABLE 14-11 **Most Common Patterns of Typical Voiding Dysfunctions Seen with Types of Neurologic Disease or Injury**

| Disorder | Detrusor Activity | Compliance | Smooth Sphincter | Striated Sphincter | Other |
|---|---|---|---|---|---|
| Cerebrovascular accident | O | N | S | S<br>±VC | There may be decreased sensation of lower urinary tract (LUT) events. |
| Brain tumor | O | N | S | S | There may be decreased sensation of LUT events. |
| Cerebral palsy | O | N | S | S<br>D (25% of those with DO)<br>±VC | |
| Parkinson disease | O<br>I | N | S | S<br>Bradykinesia | |
| Multiple system atrophy | O I | N<br>† | O | S | Striated sphincter may exhibit denervation. |
| Multiple sclerosis | O | N | S | S<br>D (30%-65%) | Dyssynergia figures refer to percentage of those with detrusor overactivity (DO). |
| **Spinal cord injury**<br>Suprasacral | O | N | S | D | Smooth sphincter may be dyssynergic if lesion is above T7. |

(*Continued*)

TABLE 14-11 **Most Common Patterns of Typical Voiding Dysfunctions Seen with Types of Neurologic Disease or Injury—Cont'd**

| Disorder | Detrusor Activity | Compliance | Smooth Sphincter | Striated Sphincter | Other |
|---|---|---|---|---|---|
| Sacral | A | N<br>† (may develop) | CNR<br>O (may develop) | F | |
| Autonomic hyperreflexia | O | N | D | D | |
| Myelodysplasia | A | N<br>O | O<br>†(MA) | F | Findings vary widely in different series. Striated sphincter commonly shows some evidence of denervation. |
| Tabes, pernicious anemia | I<br>A | N<br>‡ | S | S | Primary problem is loss of sensation. Detrusor may become decompensated secondary to overdistention. |
| Disk disease | A | N | CNR | S | Striated sphincter may show evidence of denervation and fixed tone. |
| Radical pelvic surgery | I<br>A | †<br>N | O | F | |
| Diabetes | I<br>A<br>O | N<br>‡ | S | S | Sensory loss contributes, but there is a motor neuropathy as well. |

*Detrusor activity: I, impaired; O, overactive; A, areflexia.*
*Compliance: N, normal; †, decreased; ‡, increased.*
*Smooth sphincter: S, synergic; D, dyssynergic; O, open, incompetent at rest; CNR, competent, nonrelaxing.*
*Striated sphincter: S, synergic; D, dyssynergic; ±VC, voluntary control may be impaired; F, fixed tone.*

experience smooth sphincter dyssynergia and autonomic hyperreflexia (AH). Incontinence may occur due to DO, but the outlet obstruction can also cause urinary retention.

3. **Complete spinal cord lesions at the sacral spinal cord or root level**

   Such patients generally do not manifest involuntary bladder contractions per se. Detrusor areflexia is initially the rule after spinal shock, and, depending on the type and extent of neurologic injury, various forms of decreased compliance during filling may occur. An open smooth sphincter area may result, but whether this is caused by sympathetic or parasympathetic decentralization or defunctionalization (or both or neither) has never been determined. Various types of striated sphincter dysfunction may occur, but commonly the area retains a residual resting sphincter tone (not the same as dyssynergia) and is not under voluntary control.
4. **Interruption of peripheral reflex arc**

   The dysfunctions that occur with interruption of the peripheral reflex arc may be very similar to those of distal spinal cord or nerve root injury. Detrusor areflexia often develops, low compliance may result, the smooth sphincter area may be relatively incompetent, and the striated sphincter area may exhibit fixed residual tone not amenable to voluntary relaxation. True peripheral neuropathy can be motor or sensory, with the usual expected sequelae, at least initially.

## CEREBROVASCULAR DISEASE, CVA

Thrombus, occlusion, and hemorrhage are the most common causes of stroke, leading to ischemia and infarction of variably sized areas in the brain, usually around the internal capsule. **After the initial acute episode, urinary retention from detrusor areflexia may occur.** The neurophysiology of this **"cerebral shock"** is unclear. After a variable degree of recovery from the neurologic lesion, a fixed deficit may become apparent over a few weeks or months. **The most common long-term expression of LUT dysfunction after CVA is phasic DO. Sensation is variable but is classically described as generally intact, and thus the patient has urgency and frequency with DO. The appropriate response is to try to inhibit the involuntary bladder contraction by forceful voluntary contraction of the striated sphincter. If this can be**

**accomplished, only urgency and frequency result; if not, urgency with incontinence results.**

The exact acute and chronic incidence of any LUT dysfunction after CVA, and specifically of incontinence, is not readily discernible. **Cited prevalences of UI on hospital admission for stroke generally range from 30% to 80%, on discharge from 20% to 30%, and some months later from 10% to 20%. Previous descriptions of the voiding dysfunction after CVA have all cited the preponderance of DO with coordinated sphincter activity. It is difficult to reconcile this with the relatively high incontinence rate that occurs,** even considering the probability that a percentage of these patients had an incontinence problem before the CVA. **There are two possible mechanisms: (1) impaired sphincter control and (2) lack of appreciation of bladder filling and of impending bladder contraction.** It has been reported that the majority of patients with involvement of the cerebral cortex and/or internal capsule are unable to forcefully contract their striated sphincter when an impending involuntary bladder contraction is sensed. Reduced bladder sensation has been reported in patients with global underperfusion of the cerebral cortex, especially the frontal areas.

**Detrusor underactivity or areflexia can also exist** after CVA. **True detrusor-striated sphincter dyssynergia does not occur following a CVA. Pseudodyssynergia may occur** during urodynamic testing. **Smooth sphincter function is generally unaffected** by CVA. Poor flow rates and high residual urine volumes in a male with pre-CVA symptoms of prostatism generally indicate prostatic obstruction. A urodynamic evaluation is advisable before committing such a patient to mechanical outlet reduction to exclude DHIC as a cause of symptoms.

In the functional system of classification, the most common type of LUT dysfunction after stroke would then be characterized as a failure to store secondary to bladder overactivity, specifically involuntary bladder contractions.

In the ICS Classification System, the dysfunction would most likely be classified as overactive neurogenic detrusor function, normal sensation, low capacity, normal compliance, and normal urethral closure function during storage; during voiding the description would be normal detrusor activity and normal urethral function assuming that no anatomic obstruction existed. Treatment, in the absence of coexisting significant bladder obstruction or significantly impaired contractility, is directed at decreasing bladder contractility and increasing bladder capacity (see Table 14-7).

## DEMENTIA

Dementia is a poorly understood disease complex involving atrophy and the loss of gray and white matter of the brain, particularly the frontal lobes. **When LUT dysfunction occurs, the result is generally incontinence. It is difficult to ascertain whether this is due to DO with the type of disorder of voluntary striated sphincter control mentioned with CVA or whether it is a type of situation in which the individual has simply lost the awareness of the desirability of voluntary urinary control.**

## CEREBRAL PALSY

*Cerebral palsy (CP)* is the rubric applied to a nonprogressive injury of the brain in the prenatal or perinatal period (some say up to 3 years) producing neuromuscular disability and/or specific symptom complexes of cerebral dysfunction. The etiology is generally infection or a period of hypoxia. **Most children and adults with only CP have urinary control and what seems to be normal filling and storage and normal emptying.**

The incidence of LUT dysfunction is vague because the few available series report mostly subcategorizations of those who present with LUT symptoms. In those individuals with CP who exhibit significant dysfunction, the type of damage that one would suspect from the most common urodynamic abnormalities seems to be localized anatomically above the brainstem. This is commonly reflected by phasic DO and coordinated sphincters. However, spinal cord damage can occur, and perhaps this accounts for those individuals with CP who seem to have evidence of striated sphincter dyssynergia or of a more distal type of neural axis lesion.

## PARKINSON DISEASE

This neurodegenerative disorder of unknown cause affects primarily the dopaminergic neurons of the substantia nigra, the origin of the dopaminergic nigrostriatal tract to the caudate nucleus and putamen. **Dopamine deficiency in the nigrostriatal pathway accounts for most of the classic clinical motor features of PD.** The classic major signs of PD consist of tremor, skeletal rigidity, and bradykinesia, a symptom complex often referred to as **parkinsonism.**

There are causes of parkinsonism other than PD. The combination of asymmetry of symptoms and signs, the presence of a resting tremor, and a good response to levodopa best differentiates PD from parkinsonism produced by other causes, although none of these is individually specific for PD. Multiple system atrophy (MSA; see next section) is the entity most commonly confused with PD. The following suggest MSA: (1) urinary symptoms precede or present with parkinsonism, (2) UI, (3) significant postvoid residual, (4) initial erectile failure, and (5) abnormal striated sphincter EMG.

**LUT dysfunction occurs in 35% to 70% of patients with PD.** Preexisting detrusor or outlet abnormalities may be present, and the symptomatology may be affected by various types of treatment for the primary disease. **When voiding dysfunction occurs, symptoms generally (50% to 75%) consist of urgency, frequency, nocturia, and urge incontinence.** The remainder of patients have "obstructive" symptoms or a combination. **The most common urodynamic finding is DO. The smooth sphincter is synergic. There is some confusion regarding EMG interpretation.** Sporadic involuntary activity in the striated sphincter during involuntary bladder contraction has been reported in as many as 60% of patients; however, this does not cause obstruction and cannot be termed *true dyssynergia*, which generally does not occur. **Pseudodyssynergia may occur, as well as a delay in striated sphincter relaxation (bradykinesia) at the onset of voluntary micturition, both of which can be urodynamically misinterpreted as true dyssynergia. Impaired detrusor contractility may also occur, either in the form of low amplitude or poorly sustained contractions or a combination. Detrusor areflexia is relatively uncommon in PD.**

Many cases of PD in the older literature may actually have been MSA, and citations regarding symptoms and urodynamic findings may not therefore be accurate. An example of this is the inference that transurethral resection of the prostate (TURP) in the patient with PD is associated with a high incidence of UI (because of poor striated sphincter control). Retrospective interpretation of case studies has concluded that these were patients with MSA and not PD and **that TURP should not be contraindicated in patients with PD** because striated sphincter denervation and hyopfunction are rare in PD patients. However, one must be cautious with such patients, and a complete urodynamic or video urodynamic evaluation is advisable. Poorly sustained bladder contractions, sometimes with slow sphincter relaxation, should make one less optimistic regarding the results of outlet reduction in the male with PD.

LUT dysfunction secondary to PD defies “routine” classification within any system. It is most manifest by storage failure secondary to bladder overactivity, but detailed urodynamic evaluation is mandatory before any but the simplest and most reversible therapy. The therapeutic menus (see Tables 14-7 and 14-8) are perfectly applicable, but **the disease itself may impose certain limitations on the use of certain treatments** (e.g., limited mobility for rapid toilet access, hand control insufficient for CIC).

## MULTIPLE SYSTEM ATROPHY

MSA is a progressive neurodegenerative disease of unknown etiology. The symptoms encompass parkinsonism and cerebellar, autonomic (including urinary and erectile problems), and pyramidal cortical dysfunction in a multitude of combinations. The clinical features are separable from PD.

The neurologic lesions of MSA consist of **cell loss and gliosis in widespread areas**, much more so than with PD, and this more diffuse nature of cell loss probably explains why bladder symptoms may occur earlier than in PD and be more severe and why erection may be affected as well. Affected areas have been identified in the **cerebellum, substantia nigra, globus pallidus, caudate, putamen, inferior olives, intermediolateral columns of the spinal cord, and Onuf nucleus**. Males and females are equally affected, with the onset in middle age. MSA is generally progressive and associated with a poor prognosis. **Shy-Drager syndrome** has been described in the past as characterized clinically by orthostatic hypotension, anhidrosis, and varying degrees of cerebellar and parkinsonian dysfunction. Voiding and erectile dysfunction (ED) are common. Some consider this as late-stage MSA.

**Clinical urogenital criteria favoring a diagnosis of MSA are** (1) **urinary symptoms precede or present with parkinsonism,** (2) **male ED precedes or presents with parkinsonism,** (3) **UI,** (4) **significant postvoid residual, and** (5) **worsening LUT dysfunction after urologic surgery.** The **initial urinary symptoms** of MSA are **urgency, frequency, and urge incontinence**, occurring up to 4 years before the diagnosis is made, as does erectile failure. **DO is frequently found**, as one would expect from the CNS areas affected, **but decreased compliance may occur**, reflecting distal spinal involvement of the locations of the cell bodies of autonomic neurons innervating the LUT. **As the disease progresses, difficulty in initiating and maintaining voiding may occur**, probably from pontine and sacral cord lesions, and this generally is associated with a poor prognosis. Cystourethrography or video urodynamic studies may reveal an **open bladder neck (ISD),** and many patients exhibit evidence of **striated sphincter denervation** on motor unit electromyography. The smooth and striated sphincter abnormalities predispose women to sphincteric incontinence and make prostatectomy hazardous in men.

**The treatment of significant voiding LUT caused by MSA is difficult and seldom satisfactory.** Treatment of DO during filling may worsen problems initiating voluntary micturition or worsen impaired contractility during emptying. Patients generally have sphincteric insufficiency and rarely is an outlet-reducing procedure indicated. Drug treatment for sphincteric incontinence may further worsen emptying problems. Generally, the goal in these patients is to facilitate storage, and CIC would often be desirable. Unfortunately, patients with advanced disease often are not candidates for CIC.

## MULTIPLE SCLEROSIS

MS is believed to be immune mediated and is characterized by **neural demyelination, generally characterized by axonal sparing in the spinal cord and brain**. The demyelinating process most commonly involves the lateral corticospinal (pyramidal) and reticulospinal columns of the cervical spinal cord, but involvement of the lumbar and sacral cord occurs to a lesser extent. Lesions may also occur in the optic nerve and in the cerebral cortex and midbrain, the latter accounting for the intellectual deterioration and/or euphoria that may be seen as well.

The incidence of LUT dysfunction in MS is related to the overall disability status. Of patients with MS, **50% to 90% complain of voiding symptoms at some time; the prevalence of incontinence is cited as 35% to 70%. LUT involvement may constitute the sole initial complaint or be part of the presenting symptom complex** in up to 15% of patients, usually in the form of acute urinary retention of "unknown" etiology or as an acute onset of urgency and frequency, secondary to overactivity.

**DO is the most common urodynamic abnormality** detected, occurring in 35% to 95% of cases in reported series. **Of the patients with overactivity, 30% to 65% have coexistent striated**

**sphincter dyssynergia. Impaired detrusor contractility or areflexia may also exist,** a phenomenon that can considerably complicate treatment efforts. Generally, the **smooth sphincter is synergic**. It is **also possible to see relative degrees of sphincteric flaccidity** caused by MS, which could predispose and contribute to sphincteric incontinence.

Because sensation is frequently intact in these patients, one must be careful to distinguish urodynamic pseudodyssynergia from true striated sphincter dyssynergia. Jerry Blaivas was the first to subcategorize true striated sphincter dyssynergia in patients with MS and identify some varieties that are more worrisome than others. For instance, in a female with MS, a brief period of striated sphincter dyssynergia during detrusor contraction, but one that does not result in excessive intravesical pressure during voiding, substantial residual urine volume, or secondary detrusor hypertrophy may be relatively inconsequential, whereas those varieties that are more sustained — resulting in high bladder pressures of long duration — are most associated with urologic complications. A **significant proportion of patients with MS with and without new symptoms will develop changes in their detrusor compliance and urodynamic pattern.** Caution should therefore be exercised in recommending irreversible therapeutic options.

The most common functional classification applicable to patients with LUT dysfunction secondary to MS would thus be storage failure secondary to DO. This is commonly complicated by striated sphincter dyssynergia, with varying effects on the ability to empty completely at acceptable pressures. Other abnormalities and other combined deficits are obviously possible, however. Once the dysfunction is broadly characterized, the treatment options should be obvious from the therapeutic menus (see Tables 14-7 and 14-8).

## SPINAL CORD INJURY

Altered LUT and sexual function occur frequently secondary to SCI and significantly affect quality of life; SCI patients are at risk urologically for UTI, sepsis, upper and lower urinary tract deterioration, upper and lower urinary tract calculi, autonomic hyperreflexia (dysreflexia), skin complications, and depression. Failure to properly address the LUT dysfunction can lead to significant morbidity and mortality.

1. **Spinal shock**

   Following a significant SCI, a period of decreased excitability of spinal cord segments at and below the level of the lesion occurs, referred to as *spinal shock*. There is **absent somatic reflex activity and flaccid muscle paralysis below this level. Spinal shock includes a suppression of autonomic and somatic activity, and the bladder is acontractile and areflexic with a closed bladder neck. The smooth sphincter mechanism seems to be closed and competent but nonrelaxing, except in some cases of thoracolumbar injury. Some EMG activity can generally be recorded from the striated sphincter,** and the maximum urethral closure pressure is still maintained at the level of the external sphincter zone; **however, the normal guarding reflex is absent.** Because sphincter tone exists, UI generally does not result unless there is gross overdistention with overflow. **Urinary retention is the rule**, and catheterization is necessary to circumvent this problem. Intermittent catheterization is an excellent method of management during this period.

   **If the distal spinal cord is intact but is simply isolated from higher centers, there is generally a return of detrusor contractility.** At first, such reflex activity is poorly sustained and produces only low pressure changes, but the strength and duration of such involuntary contractions increase, producing involuntary voiding, usually with incomplete bladder emptying. Spinal shock generally lasts 6 to 12 weeks in complete suprasacral spinal cord lesions but can last for as long as a year or two. It can last for a shorter period of time in incomplete suprasacral lesions and only a few days in some patients. **In evolving lesions, every attempt should be made to preserve as low a bladder storage pressure as possible.**
2. **Suprasacral SCI**

   The characteristic pattern that results when a patient has a complete lesion above the sacral spinal cord is **DO, smooth sphincter synergia (with lesions below the sympathetic outflow), and striated sphincter dyssynergia.** Neurologic examination shows spasticity of skeletal muscle distal to the lesion, hyperreflexic deep tendon reflexes, and abnormal plantar responses. There is impairment of superficial and deep sensation. The **guarding reflex is absent or weak in**

**most patients** with a complete suprasacral SCI. In incomplete lesions the reflex is often preserved but very variable.

**The striated sphincter dyssynergia causes a functional obstruction with poor emptying and high detrusor pressure. Incomplete bladder emptying may be compounded by what seems to be a poorly sustained or absent detrusor contraction. The urodynamic and upper tract consequences of the striated sphincter dyssynergia vary with severity (generally worse in complete lesions than in incomplete ones), duration (continuous contraction during detrusor activity is worse than intermittent contraction), and anatomy (male is worse than female).** Once reflex voiding is established, it can be initiated or reinforced by the stimulation of certain dermatomes, as by tapping the suprapubic area.

From a functional standpoint the voiding dysfunction most commonly seen in suprasacral SCI represents both a filling/storage and an emptying failure. Although the urodynamics are "safe" enough in some individuals to allow only periodic stimulation of bladder reflex activity, many will require some treatment. If detrusor pressures are suitably low or if they can be made suitably low with nonsurgical or surgical management, the problem can be treated primarily as an emptying failure, and CIC can be continued, when practical, as a safe and effective way of satisfying many of the goals of treatment. Alternatively, sphincterotomy, stenting, or intrasphincteric injection of botulinum toxin can be used in males to lower the detrusor leak point to an acceptable level, thus treating the dysfunction primarily as one of emptying. The resultant storage failure can be obviated either by timed stimulation or with an external collecting device. In the dexterous SCI patient, the former approach using CIC is common. Electrical stimulation of the anterior sacral roots with some form of deafferentation is also now a distinct reality.

As with all patients with neurologic impairment, a careful initial evaluation and periodic follow-up evaluation must be performed to **identify and correct the following risk factors and potential complications: bladder overdistention, high-pressure storage, high DLPP, VUR, stone formation (lower and upper tracts), and complicating infection, especially in association with reflux.**

3. **Sacral SCI**

   Following recovery from spinal shock, there is usually a depression of deep tendon reflexes below the level of the lesion with varying degrees of flaccid paralysis. Sensation is generally absent below the lesion level. **Detrusor areflexia with high or normal compliance is the common initial result. Decreased compliance may develop, a change often seen with neurologic lesions at or distal to the sacral spinal cord and most likely representing a response to neurologic decentralization.**

   The **classical outlet findings are described as a competent but nonrelaxing smooth sphincter and a striated sphincter that retains some fixed tone but is not under voluntary control**. Closure pressures are decreased in both areas. However, the **late appearance of the bladder neck may be open**. Attempted voiding by straining or Credé results in obstruction at the bladder neck (if closed) or at the distal sphincter area by fixed sphincter tone. Potential risk factors are those previously described, with particular emphasis on storage pressure, which can result in silent upper tract decompensation and deterioration in the absence of VUR. The treatment of such a patient is generally directed toward producing or maintaining low-pressure storage while circumventing emptying failure with CIC when possible. Pharmacologic and electric stimulation may be useful in promoting emptying in certain circumstances.
4. **Neurologic and urodynamic correlation in SCI**

   Although generally correct, the correlation between somatic neurologic findings and urodynamic findings in suprasacral and sacral SCI patients is not exact. A number of factors should be considered in this regard. First, whether a lesion is complete or incomplete is sometimes a matter of definition. A complete lesion, somatically speaking, may not translate into a complete lesion autonomically, and vice versa. Multiple injuries may actually exist at different levels, even though what is seen somatically may reflect a single level of injury. Even considering these situations, however, all such discrepancies are not explained.

   **Management of the urinary tract in such patients must be based on urodynamic principles and findings rather than inferences from the neurologic history and evaluation. Similarly,**

**although the information regarding "classic" complete lesions is for the most part valid, neurologic conclusions should not be made solely on the basis of urodynamic findings.**

5. **Autonomic hyperreflexia (dysreflexia, AH)**

AH is a potentially fatal emergency unique to the SCI patient. AH represents an acute massive disordered autonomic (primarily sympathetic) response to specific stimuli in patients with SCI above the level of T6 to T8 (the sympathetic outflow). It is more common in cervical (60%) than thoracic (20%) injuries. Onset after injury is variable, usually soon after spinal shock but may be up to years after injury. Distal cord viability is a prerequisite.

Symptomatically, AH is a syndrome of exaggerated sympathetic activity in response to stimuli below the level of the lesion. The **symptoms** are **pounding headache, hypertension, and flushing of the face and body above the level of the lesion with sweating. Bradycardia is a usual accompaniment,** although tachycardia or arrhythmia may be present. **Hypertension may be of varying severity,** from causing a mild headache before the occurrence of voiding to life-threatening cerebral hemorrhage or seizure. The **stimuli for this exaggerated response commonly arise from the bladder or rectum and generally involve distention**, although other stimuli from these areas can be precipitating. **Precipitation may be the result of simple LUT instrumentation, tube change, catheter obstruction, or clot retention**; in such cases, the symptoms resolve quickly if the stimulus is withdrawn. **Other causes** or exacerbating factors may include **other upper or lower urinary tract pathology (e.g., calculi), gastrointestinal (GI) pathology, long bone fracture, sexual activity, electrocoagulation, and decubiti. DO and striated sphincter dyssynergia invariably occurs, and smooth sphincter dyssynergia is generally a part of the syndrome as well, at least in males.**

The **pathophysiology** is that of a nociceptive stimulation via afferent impulses that ascend through the cord and elicit reflex motor outflow, causing arteriolar, pilomotor, and pelvic visceral spasm and sweating. Normally, the reflexes would be inhibited by secondary output from the medulla, but because of the SCI this does not occur below the lesion level.

**Ideally, any endoscopic procedure in susceptible patients should be done under spinal anesthesia or carefully monitored general anesthesia.** Acutely, the hemodynamic effects of this syndrome may be managed with α-adrenergic blocking agents, nitrates, calcium channel blockers, or angiotensin-1-converting enzyme inhibitors (ACEIs). Ganglionic blockers had previously been the mainstay of treatment, but their usage has mostly been abandoned. Various prophylactic regimens using vasodilators prior to hazardous procedures (e.g., cystoscopy, and urodynamics) are utilized and are generally institution specific.

Chronic prophylaxis with an α-1 adrenergic blocker has been recommended and found useful by some authorities. Such prophylaxis may be particularly important in view of the fact that significant elevations in blood pressure (BP) can occur without other symptoms of AH. Prophylaxis, however, does not eliminate the need for careful monitoring during provocative procedures. There are patients with severe AH that is intractable to oral prophylaxis and correction by urologic procedures. For these unfortunate individuals, a number of neurologic ablative procedures have been used — sympathectomy, sacral neurectomy, sacral rhizotomy, cordectomy, and dorsal root ganglionectomy.

## NEUROSPINAL DYSRAPHISM

Although primarily a pediatric problem, certain considerations regarding the adult with these abnormalities should be mentioned. Secondary to progress in the overall care of children with myelodysplasia, urologic dysfunction often becomes a problem of the adult with this disease. The **"typical" myelodysplastic patient** shows an **areflexic bladder with an open bladder neck. Decreased compliance may be present. The bladder generally fills until the resting residual fixed external sphincter pressure is reached, and then leakage occurs. Stress incontinence often occurs also. A small percentage of patients demonstrate DO and striated sphincter dyssynergia.**

After puberty, most male myelodysplastic patients note an improvement in continence probably due to prostatic enlargement. In adult patients, the problems encountered in myelodysplastic children still exist, but are often compounded by prior surgery, upper tract dysfunction, and one form of urinary diversion or another. In adult females, the goal is to increase urethral sphincter efficiency without causing an undue increase in urethral closing pressure, which might result in a change in bladder compliance. Periurethral injection therapy to achieve continence may give as good a result as a pubovaginal sling or artificial sphincter in this circumstance. Continence in adult male myelodysplastic individuals follows the same general rules as in females, and injectable materials may give good results in this group as well, unless the outlet is widely dilated. Dry individuals, of course, will be on intermittent self-catheterization. Nowhere is the failure of a neurologic examination to predict urodynamic behavior more obvious than in patients with myelomeningocele. The **prime directive of therapy remains the avoidance of high storage pressures.**

**Tethered cord syndrome** (**TCS**) is defined as a stretch-induced functional disorder of the spinal cord with its caudal part anchored by inelastic structures. Vertical movement is restricted. The anchoring structures can include a scar from prior surgery, fibrous or fibroadipose filum terminale, a bony septum, or tumor. Adults with TCS can be divided into those with a prior history of spinal dysraphism with a previously stabilized neurologic status who present with subtle progression in adulthood, and those without associated spinal dysraphism who present with new subtle neurologic symptoms. Symptoms can include back pain, leg weakness, foot deformity, scoliosis, sensory loss, and bowel or LUT dysfunction. TCS is reported to occur in 3% to 15% of patients with myelomeningocele. **There is no typical dysfunction in TCS**, and treatment must be based on contemporary urodynamic evaluation.

## DISK DISEASE, CAUDA EQUINA SYNDROME, AND SPINAL STENOSIS

Most **disk protrusions** compress the spinal roots in the L4-L5 or L5-S1 interspaces. Voiding dysfunction may occur as a result, and when present, generally occurs with the usual clinical manifestations of low back pain radiating in a girdlelike fashion along the involved spinal root areas. Examination may reveal reflex and sensory loss consistent with nerve root compression. The most characteristic findings on physical exam are sensory loss in the S2-4 dermatomes (perineum or perianal areas), S1-2 dermatomes (lateral foot), or both. The **incidence of voiding dysfunction in**

**disk prolapse ranges from 1% to 18%. The most consistent urodynamic finding is a normally compliant acontractile bladder associated with normal innervation or incomplete denervation of the perineal floor muscles.** There is a lower incidence of decreased compliance in root damage secondary to disk prolapse, as opposed to myelomeningocele. **Occasionally, patients may show DO**, attributed to irritation of the nerve roots.

Patients with voiding dysfunction generally present with difficulty voiding, straining, or urinary retention. It should be noted that **laminectomy may not improve bladder function, and prelaminectomy urodynamic evaluation is desirable** because it may be difficult postoperatively to separate causation of voiding dysfunction due to the disk sequelae alone from changes secondary to the surgery.

**Cauda equina syndrome** is a term applied to the clinical picture of perineal sensory loss with loss of voluntary control of both anal and urethral sphincter and of sexual responsiveness. This can occur not only secondary to disk disease (severe central posterior disk protrusion) but to other spinal canal pathologies as well. Typically, patients have an acontractile detrusor with no decreased or absent bladder sensation. The findings are variable, however, and depend of the extent and location of nerve root or cord damage.

**Spinal stenosis** is a term applied to any narrowing of the spinal canal, nerve root canals, or intervertebral foramina. It may be congenital, developmental, or acquired. Compression of the nerve roots or cord by such a problem may lead to neuronal damage, ischemia, or edema. **Spinal stenosis may occur without disk prolapse. Symptoms may range from those consequent to cervical spinal cord compression to a cauda equina syndrome with corresponding urodynamic findings.** Back and lower extremity pain, cramping, and paresthesias related to exercise and relieved by rest are the classic symptoms of lumbar stenosis caused by lumbar spondylosis and are believed to result from a sacral nerve root ischemia. The urodynamic findings are dependent on the level and the amount of spinal cord or nerve root damage.

## RADICAL PELVIC SURGERY

Voiding dysfunction after pelvic plexus injury occurs **most commonly after abdominoperineal resection and radical hysterectomy.** The **incidence** has been estimated in older literature to range from

20% to 68% of patients after abdominoperineal resection, 16% to 80% after radical hysterectomy, 20% to 25% after anterior resection, and 10% to 20% after proctocolectomy. Current incidence is most likely significantly lower because of the use of nerve-sparing techniques during these types of pelvic surgery. It has been estimated, however, that in 15% to 20% of affected individuals, the voiding dysfunction is permanent. **The injury may occur consequent to denervation or neurologic decentralization, tethering of the nerves or encasement in scar, direct bladder or urethral trauma, or bladder devascularization.** Adjuvant treatment, such as chemotherapy or radiation, may play a role as well. The type of voiding dysfunction that occurs is dependent on the specific nerves involved, the degree of injury, and any pattern of reinnervation or altered innervation that results over time.

**When permanent voiding dysfunction occurs** after radical pelvic surgery, the **pattern is generally one of a failure of voluntary bladder contraction, or impaired bladder contractility, with obstruction by what seems urodynamically to be residual fixed striated sphincter tone,** which is not subject to voluntarily induced relaxation. **Often, the smooth sphincter area is open and nonfunctional.** Whether this appearance of the bladder neck-proximal urethra is caused by parasympathetic damage or terminal sympathetic damage or whether it results from the hydrodynamic effects of obstruction at the level of the striated sphincter is debated and unknown. **Decreased compliance is common** in these patients, and this, with the “obstruction” caused by fixed residual striated sphincter tone, results in both storage and emptying failure. **These patients often experience leaking across the distal sphincter area and are unable to empty the bladder because, although intravesical pressure may be increased, nothing approximates a true bladder contraction.** The patient often presents with UI that is characteristically most manifest with increases in IAP. This is usually most obvious in females because the prostatic bulk in males often masks an equivalent deficit in urethral closure function. Alternatively, patients may present with variable degrees of urinary retention.

**Urodynamic studies may show decreased compliance, poor proximal urethral closure function, loss of voluntary control of the striated sphincter, and a positive bethanechol supersensitivity test. Upper tract risk factors are related to intravesical pressure and the DLPP, and the therapeutic goal is always low-pressure**

**storage with periodic emptying. The temptation to perform a prostatectomy should be avoided unless a clear demonstration of outlet obstruction at this level is possible.** Otherwise, prostatectomy simply decreases urethral sphincter function and thereby may result in the occurrence or worsening of sphincteric UI. **Most of these dysfunctions will be transient**, and the temptation to "do something" other than perform CIC initially after surgery in these patients, especially in those with little or no preexistent history of LUT dysfunction, cannot be too strongly criticized.

## DIABETES MELLITUS

**If specifically questioned, anywhere from 5% to 60% of patients with diabetes report symptoms of voiding dysfunction.** However, the symptoms may or may not be caused by just the diabetes. In trying to come to conclusions regarding the incidence and types of voiding dysfunction specifically from diabetes, one has to carefully discriminate between articles that consider patients referred for LUT symptoms versus those that have evaluated unselected patients from a population known to have diabetes. Cai Frimodt-Moller coined the term ***diabetic cystopathy*** to describe the involvement of the LUT by this disease. **The classic description of LUT dysfunction secondary to diabetes is that of a peripheral autonomic neuropathy that first affects sensory afferent pathways, causing the insidious onset of impaired bladder sensation. As the classic description continues, a gradual increase in the time interval between voiding results, which may progress to the point at which the patient voids only once or twice a day without ever sensing any real urgency. If this continues, detrusor distention, overdistention, and decompensation ultimately occur. Detrusor contractility, therefore, is classically described as being decreased in the end-stage diabetic bladder.**

Current evidence points to **both a sensory and a motor neuropathy** as being involved in the pathogenesis, the motor aspect per se contributing to the impaired detrusor contractility. **The typically described classic urodynamic findings include impaired bladder sensation, increased cystometric capacity, decreased bladder contractility, impaired uroflow, and, later, increased residual urine volume.** The main differential diagnosis, at least in men, is generally BOO because both conditions commonly produce a low flow rate. Pressure/flow urodynamic studies easily differentiate the two. **Smooth or striated sphincter dyssynergia generally is not seen in**

**classic diabetic cystopathy,** but these diagnoses can easily be erroneously made on a poor or incomplete urodynamic study — voiding may involve abdominal straining, which will produce an interference EMG pattern (pseudodyssynergia), and abdominal straining alone will not open the bladder neck area.

**Recent articles, however, seem to show that DO and not this "classic" diabetic cystopathy is the predominant form of LUT dysfunction.** Although it is obvious that some (or even many) of the patients with diabetes who exhibited involuntary bladder contractions may have had factors other than diabetes to account for their bladder overactivity, the importance of urodynamic study in diabetic patients before institution of therapy cannot be overemphasized.

### TABES DORSALIS AND PERNICIOUS ANEMIA

Although syphilitic myelopathy is disappearing as a major neurologic problem, **involvement of the spinal cord dorsal columns and posterior sacral roots can result in a loss of bladder sensation and large residual urine volumes and therefore be a cause of "sensory neurogenic bladder."** Another spinal cord cause of the classic "sensory bladder" is the now uncommon pernicious anemia that produced this disorder by virtue of subacute combined degeneration of the dorsolateral columns of the spinal cord.

## Common Nonneurogenic LUT Dysfunctions

### OUTLET OBSTRUCTION SECONDARY TO BPH

This is probably the most common LUT dysfunction seen by the urologist (see Chapter 15). Classically, the patient complains of hesitancy and straining to void, with the **urodynamic correlates of low flow and high detrusor pressure during attempted voiding.** This situation represents a pure failure to empty. Approximately **50% to 80% of the time, the patient with significant prostatic obstruction develops DO,** with resultant urgency, frequency, and, if the overactivity cannot be inhibited, urgency incontinence. Under such circumstances, the dysfunction becomes a combined emptying and filling and storage problem. Treatment is relief of the obstruction either by reduction of prostatic bulk or tone. **Relief of the outlet obstruction will result in the eventual disappearance of DO, where present, in approximately 70% of cases,** but this may take 6 to 12 months. However, the DO may return years later and be unrelated to outlet obstruction.

## BLADDER NECK DYSFUNCTION

Bladder neck dysfunction is characterized by an **incomplete opening of the bladder neck during voluntary or involuntary voiding.** It has also been referred to as *smooth sphincter dyssynergia, proximal urethral obstruction, primary bladder neck obstruction,* and *dysfunctional bladder neck*. The term *smooth sphincter dyssynergia* **or** *proximal sphincter dyssynergia* **is generally used when referring to this urodynamic finding in an individual with AH. The term** *bladder neck dysfunction* **more often refers to a poorly understood nonneurogenic condition first described over a century ago** but first fully characterized by Richard Turner-Warwick and associates in 1973. The dysfunction is found almost exclusively in young and middle-aged men, and characteristically they complain of long-standing voiding/emptying (obstructive) and filling/storage (irritative) symptoms. These patients have often been seen by many urologists and have been diagnosed as having psychogenic voiding dysfunction because of a normal prostate on rectal examination, a negligible residual urine volume, and a normal endoscopic prostate and bladder appearance. The differential diagnosis also includes anatomic bladder neck contracture, BPH, dysfunctional voiding, prostatitis or prostatosis, neurogenic dysfunction, and low pressure/low flow. **Objective evidence of outlet obstruction in these patients is easily obtainable by urodynamic study. Once obstruction is diagnosed, it can be localized at the level of the bladder neck by VUDS, cystourethrography during a bladder contraction, or micturitional urethral profilometry.** The diagnosis may also be made indirectly by the urodynamic findings of outlet obstruction in the typical clinical situation and in the absence of urethral stricture, prostatic enlargement, and striated sphincter dyssynergia. **Involuntary bladder contractions or decreased compliance may occur.** When prostatic enlargement develops in individuals with this problem, a double obstruction results, and Turner-Warwick applied the term ***trapped prostate*** to this entity. The lobes of the prostate cannot expand into or through the bladder neck and therefore expand into the urethra. A patient so affected generally has a lifelong history of voiding dysfunction that has gone relatively unnoticed because he has always accepted this as normal, and exacerbation of these symptoms occurs during a relatively short and early period of prostatic enlargement. **Although α-adrenergic blocking agents may provide improvement in some patients with bladder neck dysfunction, definitive relief in the male is best achieved by bladder neck incision.** In patients with this and a trapped prostate, marked relief is generally effected by a "small" prostatic resection or ablation that includes the bladder neck or a transurethral incision of the bladder neck and prostate with resection of a small amount of prolapsing prostate tissue. Such patients often note afterward that they have never voided as well as after their treatment.

## BLADDER OUTLET OBSTRUCTION IN WOMEN

The female counterpart of nonneurogenic bladder neck dysfunction in men does exist, although it is **rare.** Definitions and diagnostic criteria vary. Victor Nitti best defines BOO as radiographic evidence of obstruction between the bladder neck and the distal urethra in the presence of a sustained detrusor contraction of any magnitude, which is usually associated with a reduced or delayed urinary flow rate. Obstruction at the level of the bladder neck is diagnosed when the bladder neck is closed or narrowed during voiding. Strict pressure-flow criteria are not used to classify cases as obstructed or not obstructed. Jerry Blaivas' group defines obstruction in the woman as a persistent low, noninvasive maximum flow rate less than 12 mL/sec on repeated study combined with a detrusor pressure at maximum measured flow rate of more than 20 cm of water in a pressure-flow study. Most authors would agree that surgical treatment of this problem in women should be approached with caution because sphincteric incontinence is a significant risk.

## LOW-PRESSURE/LOW-FLOW VOIDING IN YOUNGER MEN: THE BASHFUL BLADDER

Low-pressure/low-flow voiding can be the result of a number of causes, most notably a decompensating detrusor (generally from BOO) or as a part of the syndrome known as DHIC. When this occurs in a young man, it is generally symptomatically characterized by frequency, hesitancy, and a poor stream. The entity is readily demonstrated on urodynamic assessment and with no coexisting endoscopic abnormality. The patient generally notes marked hesitancy when attempting to initiate micturition in the presence of others, and some have therefore described this condition as an "anxious bladder" or a "bashful bladder." Our experience has been similar to that of others who have stated that, in the younger unobstructed male with this condition, neither empirical pharmacologic treatment nor transurethral surgery has had any consistent beneficial effect.

## DYSFUNCTIONAL VOIDING

This syndrome, also known as *nonneurogenic/neurogenic bladder, occult voiding dysfunction*, or *Hinman syndrome*, presents the unusual circumstance of **what appears urodynamically to be involuntary obstruction at the striated sphincter level existing in the absence of demonstrable neurologic disease**. It is very difficult to prove urodynamically that an individual has this entity. This requires simultaneous pressure/flow EMG evidence of bladder emptying occurring simultaneously with involuntary striated sphincter contraction in the absence of any element of abdominal straining component, either in an attempt to augment bladder contraction or as a response to discomfort during urination. The **etiology is uncertain** and may represent a persistent transitional phase in the development of micturitional control or persistence of a reaction phase to the stimulus of LUT discomfort during voiding, long after the initial problem that caused this has disappeared. The preferred treatment is biofeedback. Intermittent catheterization may be useful, both as therapy and as an aid to facilitating the ability to voluntarily relax the striated sphincter.

## THE UNDERACTIVE BLADDER (DETRUSOR UNDERACTIVITY)

Detrusor underactivity (DU) is defined by ICS as a **contraction of reduced strength or duration resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span**. It may exist by itself or in combination with DO during filling, outlet obstruction, or both. The symptoms are indistinguishable from those of BOO. The etiology can be neurologic or myogenic, and the pathophysiology generally involves increased connective tissue and fibrosis in the detrusor.

This situation may occur after longstanding BOO or as a chronic response to overdistention due to any cause or due to neurologic injury or disease. Attempts to produce emptying pharmacologically with a cholinergic agonist and an α-adrenergic antagonist have been generally unsuccessful, and the best treatment, when necessary, is intermittent catheterization. There is always a temptation to surgically decrease bladder outlet resistance in the hopes of "tipping the balance" in favor of emptying. Although seasoned clinical judgment plays a role here, little evidence-based data generally support such an approach.

## POSTOPERATIVE RETENTION

Urinary retention can occur postoperatively for a number of reasons. **Nociceptive impulses** can inhibit the initiation of reflex bladder contraction, perhaps through an opioid-mediated mechanism or sympathetic mediated inhibition. **Transient overdistention** of the bladder can occur under anesthesia or under the influence of analgesic medication. Purely **neurologic injury** during abdominal and pelvic surgery can also occur. Generally, in the absence of neurologic injury and with proper decompression, a patient's voiding status will return pretty much to what it was prior to the surgery and anesthesia. Therefore the optimal treatment is intermittent catheterization. Return of bladder function may be facilitated by the use of an α-adrenergic antagonist. Treatment with cholinergic agonists alone has been generally unsuccessful. A male with BPH-induced BOO on the borderline of having significant voiding dysfunction may have his previously tenuous and abnormal ability to empty compromised. In these cases, outlet reduction may be justified.

## URINARY RETENTION, THE FOWLER SYNDROME IN YOUNG WOMEN

The Fowler syndrome refers particularly to a syndrome of **urinary retention in young women in the absence of overt neurologic disease.** The **typical history** is that of a woman younger than 30 years who has found herself unable to void for a day or more with no urinary urgency but increasing lower abdominal discomfort. A bladder capacity of more than 1 L with no sensation of urgency is necessary for the diagnosis. There are no neurologic or laboratory features to support a diagnosis of any neurologic disease. MRI of the brain and the entire spinal cord is normal. The urodynamic problem is **detrusor acontractility. On concentric needle electrode examination** of the striated muscle of the urethral sphincter, however, Fowler and associates described a **unique EMG abnormality that impairs sphincter relaxation.** These patients often have polycystic ovaries. Efforts to treat this condition by hormonal manipulation, pharmacologic therapy, or injection of botulinum toxin into the striated sphincter have been unsuccessful. This condition is frequently responsive to sacral neuromodulation.

## Urinary Incontinence

UI is defined as the **involuntary loss of urine.** The term is used in various ways. It may denote a symptom, a sign, or a condition. The **symptom** is generally thought of as the patient's complaint of involuntary urine loss. The **sign** is the objective demonstration of urine loss. The **condition** is the underlying cause (pathophysiology). A simple classification of the various subtypes of UI is seen in Table 14-12. The basic pathophysiology of incontinence and various related definitions are discussed earlier in this chapter.

There are situations in which urethral incontinence cannot be considered merely as an isolated abnormality of either bladder contractility or sphincter resistance. These situations, listed in Table 14-13, are more complicated to deal with because they are

TABLE 14-12 **Classification of Urinary Incontinence**

I. Extraurethral
    A. Fistula (vesicovaginal, ureterovaginal, urethrovaginal)
    B. Ectopic ureter
II. Urethral
    A. Functional
        1. Because of physical disability
        2. Because of lack of awareness or concern
    B. Bladder abnormalities
        1. Overactivity
            a. Involuntary contractions
            b. Decreased compliance
            c. Hypersensitivity with incontinence
    C. Outlet abnormalities
        1. Genuine stress incontinence (GSI)
        2. Intrinsic sphincter deficiency
        3. Urethral instability
        4. Postvoid dribbling
            a. Urethral diverticulum
            b. Vaginal pooling of urine
    D. Overflow incontinence

TABLE 14-13 **Combined Problems Associated with Incontinence**

| |
|---|
| Detrusor overactivity (DO) with outlet obstruction |
| DO with impaired bladder contractility |
| Sphincteric incontinence with impaired bladder contractility |
| Sphincteric incontinence with DO |

more difficult to diagnose and because one entity may adversely affect or compromise treatment of the other. The most common of these is **DO with outlet obstruction.** This occurs almost exclusively in the male. The incidence of DO in series of patients with outlet obstruction secondary to prostatic enlargement ranges from 50% to 80%. Treating only the DO in these patients may result in worsening symptoms. On the other hand, when the outlet obstruction is relieved in such patients, there is a high reversal rate of the bladder status, although this reversion generally takes between 1 and 6 months and may take as long as 12 months. Neil Resnick and Subbarao Yalla described the phenomenon of **DHIC**, as occurring especially in frail, elderly, incontinent patients. These patients may have significant trabeculation, but their detrusor contracts poorly during voluntary micturition. Because bladder contractility is impaired, a vigorous pharmacologic approach usually used for involuntary bladder contractions may not be appropriate for this entity.

**Sphincter incontinence in an individual with impaired bladder contractility** should alert the clinician to the possibility of the requirement of permanent CIC following surgical repair. Depending on the patient's ability and willingness to carry out intermittent catheterization, this may drastically alter an individual's usual treatment program for sphincter incontinence if the simpler, noninvasive therapeutic measures have failed. **Sphincter incontinence can coexist with DO** in a number of circumstances and with varying effects. Such bladder overactivity has been cited as one of the most common causes of "failure" of an operation for stress incontinence. Whether these urodynamic findings really do indicate that such an operation is likely to fail is an important question because an affirmative answer would mandate a very careful urodynamic evaluation in all such patients and would doubtless decrease the enthusiasm for corrective surgery in such patients who have coexistent SUI. Patients with SUI who also have decreased compliance do not seem to fare well after surgery to correct just the SUI. The decreased compliance generally does not change, and if it was refractory to nonsurgical therapy before, it will remain that way, at least in our experience.

A **variant and more complicated form of such a combination may occur following radical pelvic surgery.** Such patients may have a combination of decreased compliance with impaired bladder contractility (from the standpoint of emptying potential) with an open and nonfunctional smooth sphincter area and obstruction by residual striated sphincter tone that is not subject to voluntary induced relaxation. These patients often leak across the distal sphincter area and are unable to empty their bladders because, although they have an increased detrusor pressure, they have nothing that approximates a true coordinated and sustained bladder contraction. They often present with UI, which is characteristically most manifest with increases in IAP. This is usually most obvious in the female patient because the prostatic bulk often masks a deficit in male urethral closure function.

One additional fact with respect to definition bears mention. The traditional perspective on UI fails to account for instances in which symptoms of urinary frequency and urgency are present without the involuntary loss of urine. **Overactive bladder** (OAB) is the ICS term that describes the symptoms of **urgency, with or without urgency incontinence, usually with frequency and nocturia.** This can further be categorized as OAB wet (with UUI) or dry (without). The prevalence of OAB is approximately the same in men and women, but as a percent of overall prevalence, OAB wet is more common in women. The management (evaluation and treatment) of OAB is basically the same as that of DO.

**Prevalence rates** for the most inclusive definitions of UI **in women** 15 years and older range from 5% to 69%, with daily rates ranging from 4% to 14%. In older women, mixed and urgency incontinence predominate, whereas in younger and middle-aged women stress (effort-related) incontinence predominates. Established and suggested risk factors for UI in women include age, pregnancy, parity, obstetric factors, hormonal status, LUT symptoms, neurologic disease, hysterectomy, obesity, functional impairment, constipation, chronic respiratory disease, cognitive impairment, and smoking. Genetic factors, some related to connective tissue disorders, may also play a role. In **men** the prevalence of UI (inclusive definition) has been reported to range from 3% to 39%, with general agreement that the prevalence is less than half that in women. Urgency incontinence predominates (40% to 80%), followed by mixed UI (10% to 30%), and SUI (less than 10%). Risk factors include age, LUT symptoms and infections, functional and cognitive impairment, neurologic disorder, and prostatectomy. In general the prevalence of some UI in nursing home residents of both sexes is estimated at higher than 50%.

A summary (Third International Consultation on Incontinence in 2004) reported the annual cost of UI in the United States as $16.3 billion in 1995 dollars and $19.5 billion in 2000 dollars. In addition to the financial costs, UI imposes a significant psychosocial impact on individuals, their families, and caregivers. **Quality of life, as measured by both generic and LUT-specific indices, is adversely affected by UI to a significant degree.** The primary spheres affected are (1) self-esteem, (2) ability to maintain an independent lifestyle, (3) social interactions with friends and family, (4) activities of daily life, and (5) sexual activity. A brief description of the more common types of UI follows.

## OUTLET-RELATED INCONTINENCE IN THE FEMALE

Classically, sphincteric incontinence in the female patient had been categorized into **(1) SUI** and (2) what was originally described by McGuire and Woodside as type III stress incontinence, now referred to as *intrinsic sphincter deficiency (ISD)*. **Classical SUI** is associated with **hypermobility of the vesicourethral junction due to poor pelvic support and an outlet that is competent at rest but loses its competence only during increases in IAP. Classical ISD** describes a bladder neck and proximal urethra nonfunctional or very poorly functional at rest. **The division between these two situations, however, is not absolute, and virtually all "experts" agree that every case of sphincteric incontinence in the female involves varying proportions of SUI and ISD.** The original implication of classical ISD was that a surgical procedure designed to correct only urethral hypermobility would have a relatively high failure rate as opposed to one designed to improve urethral compression and/or coaptation.

SUI is a condition that arises from damage to muscles and/or nerves and/or connective tissue within the pelvic floor. Urethral support is important — the urethra normally being supported by the action of the levator ani muscles through their connection to the endopelvic fascia of the anterior vaginal wall. Damage to the connection between this fascia and muscle, damage to the nerve supply, or direct muscle damage can therefore influence continence. Bladder neck function is similarly important, and loss of normal bladder neck closure can result in incontinence despite normal urethral support. **In older writings, the urethra was sometimes ignored as a factor contributing to continence in the female, and the site of continence was thought to be exclusively the bladder neck. However, in approximately 50% of continent women, urine enters the urethra during increases in abdominal pressure. The continence point in these women is at the midurethra,** where urine is stopped before it can escape from the urethral meatus. With urethral hypermobility, there is weakness of the pelvic floor. During increases in IAP, there is descent of the bladder neck and proximal urethra. If the outlet opens concomitantly, SUI ensues. In the classic form of urethral hypermobility, there is rotational descent of the bladder neck and urethra. However, the urethra may also descend without rotation (it shortens and widens), or the posterior wall of the urethra may be pulled open while the anterior wall remains fixed. It should be noted, however, that **urethral hypermobility is often present in women who are not incontinent, and thus the mere presence of urethral hypermobility is not sufficient to make a diagnosis of a sphincter abnormality unless UI is also demonstrated.**

The "**hammock hypothesis**" of John Delancey proposes that **for stress incontinence to occur with hypermobility, there must be a lack of stability of the suburethral supportive layer.** This theory proposes that the effect of abdominal pressure increases on the normal bladder outlet, if the suburethral supportive layer is firm, is to compress the urethra rapidly and effectively. If the supportive suburethral layer is lax and/or movable, compression is not as effective. **ISD** denotes an **intrinsic malfunction of the outlet sphincter mechanisms.** In its most overt form, it is characterized by a bladder neck that is open at rest and a low VLPP and maximum urethral closure pressure and is usually the result of prior surgery, trauma with scarring, or a neurologic lesion. **Urethral instability** refers to the rare phenomenon of episodic decreases in outlet pressure unrelated to increases in bladder or abdominal pressure.

## OUTLET-RELATED INCONTINENCE IN THE MALE

In theory at least, categories of outlet-related incontinence in the male are similar to those in the female. In reality, there is little if any information regarding the topic of urethral instability in the male. **Sphincteric incontinence in the male is not associated with hypermobility of the bladder neck and proximal urethra but is rather more similar to what is termed *ISD* in the female.** It is generally due to prostatectomy, pelvic trauma, or neurologic diseases.

## BLADDER-RELATED INCONTINENCE IN THE FEMALE

Bladder-related abnormalities causing UI consist of either **DO or low bladder compliance.** Neurologically, involuntary bladder contractions can be due to any lesion occurring above the sacral spinal cord. The cause(s) of idiopathic DO in the female is (are) obscure. In addition to the etiologies noted previously (neurogenic voiding dysfunction), one subject that should be mentioned is the simultaneous occurrence of DO with SUI. The fact that minor or moderate components of DO, and sometimes major ones, often disappear after successful surgery for stress incontinence suggests that these two phenomena are causally related in many patients in an as yet unknown fashion.

## BLADDER-RELATED INCONTINENCE IN THE MALE

The pathophysiology of bladder-related incontinence in the male is similar to that in the female except that there is **no known association between DO and stress incontinence in the male. There is, however, a unique association of DO with BOO in the male.** The incidence of DO in males with outlet obstruction secondary to prostatic enlargement is approximately 50%. When the outlet obstruction is relieved in such patients, there is a high reversion rate of the bladder overactivity status (approximately 70%), although this reversion may take as long as 12 months.

## OVERFLOW INCONTINENCE

This is a descriptive term that denotes **leakage of urine associated with urinary retention.** This is more common in the male than female. The **primary pathophysiology is actually a failure of emptying,** leading to urinary retention with "overflow" incontinence, resulting from either continuous or episodic elevation of intravesical pressure over urethral pressure. This generally results from outlet obstruction or detrusor inactivity, either neurologic or pharmacologic in origin, or may be secondary to inadvertent overdistention of the bladder.

## MANAGEMENT OF INCONTINENCE

Management of incontinence includes the processes of evaluation and treatment. Various algorithms are available for each, ranging from the simplest to the most complicated.

What is appropriate for one patient may not be appropriate for another. The level of complexity of the evaluation and management depends, as it does for all types of voiding dysfunction, on the following:

1. The clinical problem at hand
2. The prior treatment experience(s)
3. The patient's desire for treatment
4. The patient's goals of therapy
5. The patient's desire to avoid invasive procedures and/or complications
6. The patient's ability and desire to follow instructions or carry out specific tasks
7. The expected level of improvement under optimal circumstances
8. The healthcare provider's level of expertise
9. Environmental considerations
10. Economic considerations

## Treatment of LUT Dysfunction

### GENERAL

There are only a discrete number of therapies available, and these are easily categorized on a functional "menu" basis according to whether they are used primarily to facilitate urine storage or emptying and whether their primary effect is on the bladder or the outlet (see Tables 14-7 and 14-8). The algorithms for the management of UI in various populations endorsed by the fifth International Consultation on Incontinence (ICI) (2012) are reproduced in Tables 14-e1, 14-e2, 14-e3, 14-e4, 14-e5, 14-e6, and 14-e7. The letter grades in the tables refer to the various committee assessments using the Oxford Guidelines (Table 14-e8) adopted by the ICI. For any especially interested in this area, the most recent two-volume text is highly recommended (Abrams et al, 2013). Brief comments will be made about selected, more commonly used categories, as well as for therapies that may be gender specific. Specific therapy for BPH is considered in Chapter 15.

Note that inclusion in the lists does not necessarily imply majority agreement on efficacy. **Treatment should always begin with the simplest most reversible form(s) of therapy, proceeding gradually up the ladder of complexity, with the knowledge that it is**

**only the patient (and/or family) who is (are) empowered to say when "enough is enough." A perfect result need not be achieved. Satisfaction and avoidance of adverse outcomes are the goals. At every step, the patient and/or family must understand the potential benefits, practicalities, and risks of further therapy.**

## THERAPY TO FACILITATE BLADDER FILLING AND URINE STORAGE

1. **Inhibiting bladder contractility, decreasing sensory input, and increasing bladder capacity** (see Table 14-7)
   a. *Behavioral therapy, behavioral modification*, **and** *bladder training*

   These terms are sometimes used interchangeably in describing nonmedical, nonsurgical methods to treat various types of LUT dysfunction. The term ***behavioral therapy*** in our center includes (1) patient education about LUT function; (2) information about lifestyle changes or dietary modification (e.g., fluid restriction, avoidance of irritants); (3) so-called *bladder training* or *retraining*, which includes instituting intervals of timed voiding and gradually increasing these intervals; (4) pelvic floor physiotherapy with or without biofeedback, both to strengthen the pelvic floor musculature and to aid in the individual's ability to shut off an unwanted bladder contraction; and (5) for physically or mentally challenged individuals, scheduled toileting and/or prompted voiding. In patients with OAB, the pelvic floor physiotherapy is used primarily as an aid to patients in suppressing urgency and DO. They are taught to do "quick flicks" of the pelvic floor musculature in an effort to accomplish this. Putting all these things together involves establishing a regimen for the patient and combining all of these modalities, such that the patient voids according to a timed schedule that he or she can initially maintain. A bladder diary is an important part of this regimen and is useful in following the patient's progress. Periodically, the patient is asked to increase the intervals between micturition until an acceptable interval is reached without the symptoms of urgency or urgent incontinence interfering.

   **Biofeedback** is a technique that provides visual and/or auditory signals to an individual with respect to his or her performance of a physiologic process, in this case pelvic floor muscle contraction. Electromyography or vaginal pressure measurements are generally used. Despite the logic of biofeedback, some comprehensive reviews have failed to demonstrate the superiority of pelvic-floor muscle-exercise instruction with biofeedback over pelvic-floor exercise instruction alone. It is clear, however, that, whether considering stress, urge, or mixed UI, and using the number of incontinence episodes or the amount of urine lost as primary outcome indicators, behavioral therapy is capable of causing a significant reduction. Quoted figures range from 40% to 80%. We think of behavioral therapy as an overall program that can be used for the treatment of UI or bladder overactivity without UI. With sphincteric-related incontinence, obviously the patient should concentrate more on pelvic-floor physiotherapy for the purpose of strengthening the pelvic-floor musculature. With the OAB, with or without urge incontinence, the patient should concentrate more on the behavioral modification, using pelvic-floor physiotherapy more as a tool to abort involuntary bladder contractions. Biofeedback is optional in either case. Weight loss in the overweight population can improve both SUI and UUI and should be a part of behavioral therapy where applicable. The success of behavioral therapy (modification) is proportional to the skill and experience of the therapist and the "hands-on" time the therapist spends with the patient.

b. **Pharmacologic therapy**

In general, drug therapy for LUT dysfunction is hindered by a concept that can be expressed in one word: ***uroselectivity,*** a term originated by Karl-Erik Andersson. For instance, the clinical utility of available **antimuscarinic agents** is limited by their lack of selectivity, responsible for the classic peripheral antimuscarinic side effects of dry mouth, constipation, blurred vision, tachycardia, and/or effects on cognitive function. **Calcium channel blockers, potassium channel openers, and sensory antagonists** would be ideal for the treatment of OAB if a receptor or channel could be found that was bladder specific. At the Fifth International Consultation on Urinary Incontinence, the committee on pharmacology "graded" the various drugs used for the treatment of UI according to the Oxford system (Table 14-14).

1) **Antimuscarinic agents**

The physiologic basis for the use of anticholinergic agents is that the major portion of the neurohumoral

TABLE 14-14 **Drugs Used in the Treatment of LUTS, OAB, and DO Assessments According to the Oxford System (Modified)**

| | Level of Evidence | Grade of Recommendation |
|---|---|---|
| ***Antimuscarinic Drugs*** | | |
| Atropine, hyoscyamine | 3 | C |
| Darifenacin | 1 | A |
| Fesoterodine | 1 | A |
| Imidafenacin | 1 | B |
| Propantheline | 2 | B |
| Solifenacin | 1 | A |
| Tolterodine | 1 | A |
| Trospium | 1 | A |
| ***Drugs with Mixed Actions*** | | |
| Oxybutynin | 1 | A |
| Propiverine | 1 | A |
| Flavoxate | 2 | D |
| ***Drugs Acting on Membrane Channels*** | | |
| Calcium antagonists | 2 | D |
| K-channel openers | 2 | D |
| ***Antidepressants*** | | |
| Imipramine | 3 | C |
| Duloxetine | 2 | C |
| ***Alpha-AR Antagonists*** | | |
| Alfuzosin | 3 | C |
| Doxazosin | 3 | C |
| Prazosin | 3 | C |
| Terazosin | 3 | C |
| Tamsulosin | 3 | C |
| Silodosin | 3 | C |
| Naftopidil | 3 | C |
| ***Beta-AR Antagonists*** | | |
| Terbutaline (beta 2) | 3 | C |
| Salbutamol (beta 2) | 3 | C |
| Mirabegron (beta 3) | 1 | B |
| ***PDE-5 Inhibitors***+ | | |
| (Sildenafil, Tadalafil, Vardenafil) | 1 | B |
| ***COX-inhibitors*** | | |
| Indomethacin | 2 | C |
| Flurbiprofen | 2 | C |

*(Continued)*

TABLE 14-14 **Drugs Used in the Treatment of LUTS, OAB, and DO—Cont'd**

| | Level of Evidence | Grade of Recommendation |
|---|---|---|
| ***Toxins*** | | |
| Botulinum toxin (neurogenic)*** | 1 | A |
| Botulinum toxin (idiopathic)*** | 1 | B |
| Capsaicin (neurogenic)** | 2 | C |
| Resiniferatoxin (neurogenic)** | 2 | C |
| ***Other Drugs*** | | |
| Baclofen* | 3 | C |
| ***Hormones*** | | |
| Estrogen | 2 | C |
| Desmopressin# | 1 | A |

+ Male LUTS/OAB

* Intrathecal

** Intravesical

*** Bladder wall

# Nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases, with permission.)*

stimulus for physiologic and presumably involuntary bladder contraction is acetylcholine-induced stimulation of postganglionic parasympathetic cholinergic receptor sites on bladder smooth muscle.

In patients with OAB, the effects have been described as follows: (1) increase in the volume to the first involuntary bladder contraction, (2) decrease in the amplitude of involuntary bladder contractions, (3) increase in total bladder capacity, and (4) decrease in urgency and urgency incontinence episodes.

The common view is that in overactive bladder-related detrusor overactivity (OAB-DO), these drugs act by blocking the muscarinic receptors on the detrusor muscle that are stimulated by acetylcholine, released from activated cholinergic (parasympathetic) nerves. Thereby they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity; during this phase, there is normally no parasympathetic input to the LUT. Antimuscarinic drugs increase and anticholinesterase inhibitors decrease bladder capacity. Because antimuscarinic drugs do seem to affect the sensation of urgency during filling, this suggests an ongoing acetylcholine-mediated stimulation of detrusor tone. If this is correct, agents inhibiting acetylcholine release or activity would be expected to contribute to bladder relaxation or the maintenance of low bladder tone during filling with a consequent decrease in filling and storage symptoms unrelated to the occurrence of an involuntary contraction. Outlet resistance, at least as reflected by urethral pressure measurements, does not seem to be clinically affected. High doses of antimuscarinics can produce urinary retention in humans, but in the dose range needed for beneficial effects in OAB-DO, there is little evidence for a significant reduction of the voiding contraction in normal individuals.

The only instance in which inhibition of efferent-induced bladder contraction is a positive consideration is in the patient with neurogenic DO who wets between intermittent catheterizations. In our experience it usually takes a higher-than-recommended dose of antimuscarinics to "quiet" the bladder and achieve continence between catheterizations. The pure antimuscarinics (and drugs with combined actions — see next section) and their "ratings" by the ICI are seen in Table 14-14.

There are many claims regarding superiority of one agent over another in terms of efficacy, tolerability, and safety. One must be careful to separate theoretical "edges" (marketing) from real ones.

2) **Agents with combined action**

A number of agents, grouped under the somewhat exotic term *musculotropic relaxant* or *antispasmodic*, are promoted as having more than an antimuscarinic action. These additional actions include smooth muscle inhibition at a site metabolically distal to the cholinergic receptor mechanism and what are referred to as *local anesthetic properties*. The former action may relate to some calcium channel blocking activity. It should be noted that these latter two activities can be demonstrated in vitro, but it is doubtful that, when administered orally, either of these activities contributes to the clinical efficacy of such agents; the efficacy is most likely due simply to the fact that the 1-A drugs in this category (see Table 14-14) are good antimuscarinic agents.

3) **Beta-adrenergic (β-AR) agonists**

Three cloned subtypes of β-ARs ($\beta_1$, $\beta_2$, $\beta_3$) have been identified in the detrusor of most species, including humans. Studies have revealed a predominant expression of $\beta_3$-AR in human detrusor muscle. The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species is activation of adenylyl cyclase with subsequent formation of cyclic adenosine monophosphate (cAMP). However, there is evidence suggesting that in the bladder K+channels, particularly $BK_{Ca}$ channels, may be more important in β-AR mediated relaxation than cAMP. However, there is also evidence of inhibition of filling-inducing activity in both mechanosensitive Aβ and C-fiber primary bladder afferents, at least with mirabegron.

The in vivo effects of $\beta_3$-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), $\beta_3$-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume.

The selective $\beta_3$-AR agonist mirabegron, has been approved for treatment of OAB in the United States, Japan, and Europe. There are proof-of-concept studies for other $\beta_3$-AR selective agonists, but none of these is ready for clinical approval submission.

In the OAB patients, mirabegron consistently improves mean number of micturitions and reduces the number of urgency incontinence episodes. It has been shown also to increase mean voided volume per micturition. There have been no adverse effects on flow rate or detrusor contractibility during voluntary emptying. At this point there has been no increase over placebo reported for dry mouth, constipation, hypertension, or other clinically significant adverse cardiovascular side effects. There are certain clinical scenarios in which a $\beta_3$ agonist may be preferable as first-line treatment for OAB. Logic would also raise the possibility that an antimuscarinic plus a $\beta_3$ agonist may prove to be more efficacious than either alone. This is a clinical question awaiting an evidence base, the obvious concern being an increase in certain adverse events, particularly cardiovascular.

4) **Phosphodiesterase (PDE) inhibitors**

Drugs stimulating the generation of cAMP and cyclic guanosine monophosphate (cGMP) are known to relax smooth muscles, including the detrusor. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscle should then be a logical approach. Several well designed and conducted randomized controlled trials have confirmed that PDE inhibitors used for the treatment of ED also improve urinary symptom scores. The exact mechanism(s) behind the clinical effect and the site(s) of action are as yet unknown. Although tadalafil is approved by the FDA for the treatment of LUTs due to benign prostatic obstruction, more extensive and long-term experience with PDE inhibitors in the treatment of OAB symptoms is lacking.

5) **Tricyclic antidepressants**

The tricyclic antidepressants have been found by some to be useful agents for facilitating urine storage by both decreasing bladder contractility and increasing outlet resistance. There is disagreement about the latter function but general agreement about their utility in decreasing bladder contractility. All of these agents possess varying degrees of three major pharmacologic actions: (1) they block the active transport system responsible for the reuptake of released amine neurotransmitters serotonin and norepinephrine; (2) they have central and peripheral anticholinergic effects at some but not all sites; and (3) they are sedatives, an action that occurs, presumably, on a central basis but is perhaps related to antihistaminic properties. At histamine receptors, however, they also are antagonistic to some extent. Imipramine has prominent systemic anticholinergic effects but only a weak antimuscarinic effect on bladder smooth muscle. This action could be mediated centrally because an increase in serotonin concentration in the spinal cord could cause a decrease in bladder contractility, or it could be related to a direct inhibitory effect on bladder smooth muscle itself. In any case, the effects of imipramine on bladder smooth muscle do not appear to be mediated by an antimuscarinic effect. There may be a rationale for combining the use of such agents with an antimuscarinic drug before abandoning pharmaceutical treatment in cases where antimuscarinics or agents with combined actions have not produced the desired effect. If imipramine or any of these agents is to be utilized one must pay careful attention to the adverse event profile, especially the potential for serious cardiac effects. The current use of such agents for treatment of OAB is infrequent.

6) **Intravesical therapy to decrease bladder contractility**

One way of achieving a more bladder-selective response is to administer a drug intravesically. This has been easily done in the laboratory with multiple agents and has been done clinically with oxybutynin.

Most series are small but report definite beneficial effects with seemingly fewer side effects. Although the drug is absorbed into the circulation and effective serum levels can be measured, the first-pass metabolism through the liver is less. It is thought that the primary liver metabolite of oxybutynin is responsible in large part for the side effects, and thus these would be less using this mode of administration. This is obviously cumbersome, requires catheterization to carry out, and there is no intravesical preparation of oxybutynin. Tablets must generally be dissolved in a vehicle to accomplish this. It may be, however, that with this mode of administration, those drugs with a theoretical combined action would be able to exert some direct effect on smooth muscle because of the high local concentration, whereas with oral administration they would not.

7) **Botulinum toxin**

**Botulinum A toxin** (BoNT) is an inhibitor of the release of acetylcholine and probably other neurotransmitters at the neuromuscular junctions of autonomic nerves in smooth muscle and of somatic nerves in striated muscle. It does this by interacting with the protein complex necessary for docking vesicles. This results in decreased muscle contractility and muscle atrophy at the injection site. A sensory blockade also seems to occur. The chemical denervation is reversible, and regeneration takes place over 3 to 9 months. There are seven subtypes of BoNT; subtype A has the longest duration of action. Its use is approved in the United States as the proprietary Botox. The intradetrusor injection of BTX-A has been reported by a number of investigators to be efficacious and safe in the treatment of both neurogenic and idiopathic DO. Dosage schedules and sites of injection vary, and a careful read of the source articles is recommended (e.g., Andersson and Wein, Chapter 68, *Campbell-Walsh Urology,* 10th edition). The botulinum toxin molecule cannot cross the blood-brain barrier. A potential side effect is spread to nearby muscles, particularly when high volumes are used. Distant effects can also occur, but distant or generalized weakness due to intravascular spread is very rare. Caution is recommended in those with disturbed neuromuscular transmission or on treatment with aminoglycosides.

8) **Desmopressin**

This is a synthetic vasopressin analogue that lacks significant vasoconstrictor action. It does exert a pronounced antidiuretic effect. It is widely used as a treatment for primary nocturnal enuresis and can be useful in adults with significant and bothersome nocturia, specifically those with nocturnal polyuria. Attention should be paid to its adverse event profile, particularly the possibility of hyponatremia, especially in the elderly.

9) **Drugs affecting sensory input**

One attractive modality of therapy for OAB and bladder hypersensitivity, especially in an individual who retains the ability to voluntarily initiate a detrusor contraction, is to depress sensory neurotransmission. **Capsaicin** is the active ingredient of red peppers and, in sufficiently high concentrations, causes desensitization of C-fiber sensory afferents by initially releasing and emptying the stores of neuropeptides, which serve as sensory neurotransmitters and then by blocking further release. C-fiber afferents act as the primary sensory pathway in patients with voiding dysfunction secondary to SCI, some other neurologic diseases, and in response to other noxious stimuli. Because of the initial release of neuropeptides after intravesical administration of the drug, capsaicin causes intense local symptomatology and often requires anesthesia for administration. In addition, although beneficial effects have been reported, these effects are not universal, although positive effects, when they result, have been reported to last for 2 to 7 months. **Resiniferatoxin (RTX)** is a compound with effects similar to those of capsaicin and is approximately 1000 times more potent than capsaicin in producing desensitization, but only 100 to 300 times more potent in producing inflammation. Available information suggests intravesical therapy may be effective in both neurogenic and idiopathic DO. At present, apparent formulation and supply problems seem to have hindered further investigations.

10) **Estrogens**

There are a number of theoretical reasons that estrogens may be useful in the treatment of postmenopausal women with both bladder- and outlet-related incontinence and in the treatment of the symptoms of OAB without incontinence. Estrogens have been used for years in this manner; however, few controlled trials have been performed to confirm that estrogen is of benefit. Estrogen has an important physiologic effect on the female LUT, and its deficiency may be an etiologic factor in the pathogenesis of a number of conditions. However, **the use of estrogens alone to treat UI has given disappointing results.** In fact, menopausal systemic hormone therapy increases the risk for UI. Both estrogen plus progestin and estrogen alone decrease risks for fractures but increase risks for stroke, thromboembolic events, gallbladder disease, and UI. Estrogen plus progestin also increases the risk for breast cancer and probable dementia, whereas estrogen alone decreases the risk for breast cancer. The differences, though significant, are numerically small.

Whether local administration (vaginal) can produce beneficial LUT change is a question waiting to be answered in a double-blind controlled manner. If a positive response results for stress or urge incontinence or for symptoms of OAB without incontinence, the proper dosing schedule and preparation need to be established along with proof that local therapy does not carry the apparent risk of systemic administration.

c. **Electrical stimulation**

Electrical stimulation (ES) has been utilized in three areas of treatment for LUTS: 1) to inhibit bladder contractibility and urgency; 2) to increase sphincter resistance; and 3) to facilitate bladder contraction in certain cases of urinary retention.

1) **Neuromodulation: Sacral neuromodulation (SNM)**

This refers to the use of mild electrical impulses to stimulate the sacral nerve roots associated with voiding function (primarily S-3) with resultant modulation of voiding and continence reflex pathways. The exact mechanism of action is unknown; for suppression of DO, the locus of modulation and "readjustment" is thought to be the CNS after activation of afferent pathways. SNM involves a two-stage procedure: placement of a temporary or permanent lead for external stimulation with a test period, followed, if successful results occur, by implantation of a subcutaneous pulse generator capable of being activated by a programmable external unit. This was FDA approved as the InterStim system in 1997 for refractory urinary urge incontinence (UUI) and for urgency-frequency syndrome and nonobstructive urinary retention in 1999. Depending on the definitions utilized, initial success rates have ranged from 40% to 80% in this difficult group of patients with refractory storage conditions. Adverse events do occur, and potential patients must be made aware of these.

2) **Posterior tibial nerve stimulation (PTNS)**

This is another type of ES utilized for DO and OAB symptomatology. The posterior tibial nerve contains fibers that originate from the same sacral roots that innervate the bladder. Activation of these is achieved by a percutaneous needle activated by a low-voltage stimulator. Treatment includes weekly sessions of 30 minutes for 8 to 12 weeks followed, in some centers if effective, by maintenance sessions every 4 to 6 weeks. Reasonable success, albeit with relatively short-term follow-up, has been achieved. Obviously a transcutaneous stimulator would be a great step forward.

3) **Other forms of ES**

The success of SNM and PTNS for storage disorders has prompted the investigation of ES on other nerves, stimulation of which has been shown to affect LUT function (e.g., pudendal and dorsal genital). Acupuncture has been utilized as well, and the principle may be the same.

d. **Interruption of innervation**

Subarachnoid block is no longer used for urologic indications. Historically, this was used to convert a state of severe somatic spasticity to flaccidity and to abolish AH. As a byproduct, DO was acutely converted to areflexia. The obvious disadvantage of this type of procedure was a lack of neurologic selectivity. Additionally, the conceptually simple result of an areflexic bladder with normal compliance very often was not maintained, as decreased compliance occurred.

1) **Sacral rhizotomy and selective sacral rhizotomy**

Selective sacral rhizotomy was originally introduced as a treatment to increase bladder capacity by trying to abolish only the motor supply responsible for involuntary bladder contractions. Nonselective sacral rhizotomy often affected sphincter, sexual, and lower extremity function. There was still a problem in obtaining a truly selective result, and this procedure has fallen out of favor. Deafferentation using a **dorsal** or **posterior rhizotomy** is generally used as a part of an overall plan to simultaneously rehabilitate storage and emptying problems in patients with significant spinal cord injury or disease. Electrical stimulation may be used to produce bladder emptying as well. **Dorsal root ganglionectomy** has also been mentioned in this regard. Surgical treatment of bladder overactivity by peripheral bladder denervation was popularized in the early 1980s. A variety of techniques were proposed to partially or totally denervate (or more correctly neurologically decentralize) the bladder. These have been largely abandoned because, although some of these techniques had a high initial success rate in controlling bladder overactivity and related incontinence, the relapse rate was quite high. In addition, the long-term response to the neurologic procedure was sometimes associated with a type of neural plasticity, resulting in decreased bladder compliance.

e. **Augmentation cystoplasty**

Creation of a low-pressure, high-capacity bladder reservoir by incorporation of a detubularized bowel segment is an important modality of treatment in LUT reconstruction and in the treatment of refractory filling and storage problems. Adequate reservoir function can generally be achieved. Complications can arise including inadequate emptying or urinary retention, mucus accumulation and stones, electrolyte imbalance, recurrent infection, and the possibility of rare malignant change. Contraindications to augmentation enterocystoplasty include (1) urethral disease precluding intermittent catheterization, (2) unwillingness or inability to perform intermittent catheterization, (3) renal failure, (4) significant bowel disease, and (5) poor medical status precluding surgery. **Autoaugmentation** or **detrusor myomectomy** refers to a procedure whose purpose is to increase bladder capacity by, in essence, creating a large bladder diverticulum by removal of a section of the outer layer of the bladder wall down to the mucosa. This has the obvious advantage of not requiring bowel resection and anastomosis, but opinion is divided as to the efficacy of this procedure in increasing reservoir function in adults.

2. **Increasing outlet resistance**
   a. **Pelvic floor muscle training (PFMT)**

   Although behavioral therapy without pelvic floor physiotherapy has been shown to significantly reduce the incidence and amount of stress incontinence in females, the **portion of a behavioral therapy program that has received most attention for sphincteric incontinence is pelvic floor muscle training.** The literature is remarkably consistent in describing a significant improvement rate in 50% to 65% of patients treated with PFMT, sometimes known as *Kegel exercises* (after Arnold Kegel, a gynecologist). For hypermobility-related stress incontinence in the female and for stress incontinence in the male, it is certainly worthwhile to try pelvic floor exercise along with the rest of the behavioral therapy program as an initial or adjunctive form of treatment. For female patients with a significant element of ISD, and for males with gross urinary leakage, it is conceptually doubtful whether significant improvement would occur in even a minority of such patients. However, it is also certain that such therapy would not hurt either, and such exercises may in fact allow the individual to be able to exert greater control over the detrusor reflex as well. As mentioned previously, it has never been objectively shown whether biofeedback, using either EMG or pressure displays, adds to careful and periodic personal instruction and supervision.

   b. **Electrical stimulation**

   **Intravaginal** and **anal electrical stimulation** have been reported to treat storage failure by increasing outlet resistance and decreasing bladder contractility. In this case, the mechanism is said to involve stimulation of the striated pelvic floor musculature through branches of the pudendal nerve. Most reviews have come to the conclusion that no consistent objective evidence supports the value of pelvic floor physiotherapy plus ES over pelvic floor physiotherapy alone in the general population of patients with sphincteric incontinence. It may be that some subgroups might benefit (i.e., those who are unable to isolate their pelvic floor muscles and who therefore cannot correctly perform PFMT).

c. **Pharmacologic therapy**

1) **Alpha-adrenoreceptor agonists**

The theoretical basis for pharmacologic therapy of sphincteric incontinence is the preponderance of α-adrenergic receptor sites in the smooth muscle of the bladder neck and proximal urethra. When stimulated, these should produce smooth muscle contraction. Such stimulation can alter the urethral pressure profile by increasing maximum urethral profile and maximum urethral closure pressure. Historically, α-adrenergic agonists (such as ephedrine and phenylpropanolamine) lack selectivity for urethra alpha receptors and may increase BP and cause sleep disturbances, headache, tremor, and palpitations. Although there are reports in the literature of efficacy with these agents, the Committee on Pharmacology of the Fifth International Consultation on Incontinence did not recommend any of these agents for the treatment of stress incontinence (Table 14-15).

2) **Estrogen**

As previously described, systemic menopausal estrogen therapy is not recommended for use to treat UI of any type (see Table 14-15).

TABLE 14-15 **Drugs Used in the Treatment of Stress Incontinence**
Assessments According to the Oxford System (Modified)

| **Drug** | **Level of Evidence** | **Grade of Recommendation** |
|---|---|---|
| Clenbuterol | 3 | C |
| Duloxetine | 1 | B |
| Ephedrine | 3 | D |
| Estrogen | 2 | D |
| Imipramine | 3 | D |
| Methoxamine | 2 | D |
| Midodrine | 2 | C |
| Norephedrine (phenylpropanolamine) | 3 | D |

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases, with permission.)*

3) **Antidepressants**

Imipramine, among several other pharmacologic effects (see earlier discussion), inhibits the reuptake of norepinephrine and 5-hydroxytryptamine (5-HT) in adrenergic nerve endings. In the urethra, this can be expected to enhance the contractile effects of endogenous norepinephrine on urethral smooth muscle. Theoretically, such an action may also influence the striated muscles in the urethra and pelvic floor by effects on the spinal cord level (Onuf nucleus). Imipramine can cause a wide range of potentially dangerous side effects, especially regarding the cardiovascular system, and should be used with caution. No randomized controlled trials on the effects of imipramine in SUI seem to be available. The Fifth ICI recommends against such usage.

**Duloxetine hydrochloride,** a combined norepinephrine and serotonin reuptake inhibitor, has been shown to significantly increase urethral sphincter muscle activity during the filling/storage phase of micturition in a cat model. Bladder capacity was also increased in this model, both effects mediated centrally through motor efferent and sensory afferent modulation. There are several randomized controlled trials documenting the efficacy of duloxetine in the treatment of stress incontinence. “Cure” and improvement rates exceed those of placebo, but adverse events do as well and to a higher degree, and persistence has been a problem with moderate to severe incontinence (more than 15 episodes per week. Duloxetine is licensed in Europe for treatment of SUI in women. It was withdrawn from the FDA consideration process in the United States, although it is available at a lower dose for treatment of major depressive disorder, diabetic peripheral neuropathic pain, generalized anxiety disorder, fibromyalgia, and chronic musculoskeletal pain.

d. **Vaginal and perineal occlusive and supportive devices and urethral plugs**

Support of the bladder neck in the female resulting in improved continence is possible with intravaginal devices that have not been reported to cause significant

LUT obstruction or morbidity. Tampons, traditional pessaries and contraceptive diaphragms, and intravaginal devices specifically designed for bladder neck support have been used. Ideally, **support devices** would reduce any degree of vaginal prolapse and, by supporting the anterior vaginal wall and therefore the urethrovesical junction and bladder neck, control incontinence. Although most individuals would agree that information about vaginal support devices should be included in the treatment options when counseling women with SUI, most would also agree that studies performed on these devices in the acute laboratory setting demonstrate better performance than diary-based studies with respect to the amount and number of episodes of leakage. It is also generally agreed that such devices work best in individuals with minimal to moderate leakage. Pessary usage seems most effective and most common in elderly women with a major degree of anterior vaginal wall prolapse and hypermobility-related stress incontinence.

**Occlusive devices** can be broadly divided into external and internal devices, referring to whether the device itself occludes the urethra or bladder neck from the outside or has to be inserted per urethra. **There have been many patterns of external occlusive devices available for use in the male,** but all seem to take the form of a clamp that is applied across the penile urethra. The Baumrucker and Cunningham clamps are basically double-sided foam cushions that squeeze the penile urethra between the two arms. The Baumrucker clamp uses a Velcro-type system. Another type of compression device that is size adjustable encircles the penis and stops the flow of urine when it is inflated with air. Soft tissue damage by excess compression can occur with these clamps, and thus their use is extremely risky in patients with sensory impairment. Their prime use is in patients with sphincteric incontinence, although if applied tightly enough, the patient can occlude the urethra under any circumstances — although with a distinct danger of retrograde pressure damage. Occlusive devices for **female sphincteric incontinence** have been mentioned (and mostly discarded) since the late 1700 s. Multiple **intravaginal occlusive devices** have been described, all of which historically consisted of rather bizarre-looking configurations of silicone and plastic with a dual purpose: to stay in the vagina and to compress the urethra. None of these seem to have stood the test of time. Another interesting concept that proved to be poorly functional was an inflatable pad held firmly against the perineum by straps attached to a waistband, fitted to the individual patient. Inflation of the pad with a cuff resulted in an elevation and compression of the perineum. The simplest of the more recently introduced devices is a **continence control pad** or **external urethral occlusion device.** A hydrogen-coated foam pad is placed over the external urethral meatus. Another type of device is a **meatal suction** or **occlusion device.** The concept is to create by suction a measured amount of negative pressure, causing coaptation of the urethral wall. Neither has achieved popularity.

**Intraurethral devices** are inserted into the urethra to block urinary leakage. Similarities among these devices include (1) a means to prevent intravesical migration (a meatal plate or tab at the meatus), (2) a mechanism to maintain the device in its proper place in the urethra (spheres, inflatable balloons, or flanges on the proximal end); and (3) a device or mechanism to permit removal for voiding (a string or pump). Most patients utilizing external meatal occlusive devices or intraurethral devices have reported dryness or improvement in the laboratory and on diaries. Long-term results, however, are limited, and the exact place of this therapy in the algorithm of conservative management of female sphincteric incontinence has not yet been determined. Certainly, the use of these devices is grossly out of proportion (lower) to the initially positive and optimistic reports in the literature.

The characteristics of an ideal occlusive or supportive device would include (1) efficacy; (2) comfort; (3) ease of application, insertion, and removal; (4) lack of interference with adequate voiding; (5) lack of tissue damage; (6) lack of infection; (7) no compromise of subsequent therapy; (8) cosmetic acceptance (unobtrusive); and (9) lack of interference with sexual activity. Reasons for failure include (1) the patient's reluctance to “put anything inside me or on me”; (2) inconvenience (frequent removal and self-insertion with a requirement for periodic replacement by the healthcare provider); (3) discomfort, real or perceived; (4) fear of infection and/or bleeding; (5) association of such devices by the patient with “last resort” remedies and the implications which that association raises; (6) unwillingness to pay out of pocket for these (poor coverage for these devices); (7) perceived lack of long-term success; and (8) nonincentive for the healthcare provider to promote the devices, except in a capitated environment.

e. **Nonsurgical periurethral compression (bulking)**

Urethral bulking is a minimally invasive treatment option for SUI that can be effective in well selected patients. It is believed to work by promoting mucosal coaptation due to the injection of material to “bulk” or thicken the submucosal layer of the urethra. The procedure was first described in 1938 but it wasn’t until the introduction of collagen as an injectable implant material that it became highly utilized. Traditionally, urethral bulking was reserved for patients with intrinsic sphincter deficiency in the absence of urethral hypermobility. Generally this was proven urodynamically with low ALPPs of less than 90 cm $H_20$. Because of the minimally invasive nature of the procedure and the low complication rate, use was extended to patients with all types of SUI. In the current era, however, the higher efficacy of the synthetic midurethral sling, combined with its minimal morbidity compared with the prior surgical options, has lessened the interest and enthusiasm for bulking therapy. Nonetheless, bulking may be an appropriate treatment option for some patients. These include poor surgical candidates such as the frail elderly, patients with poor detrusor contractility putting them at high risk for postoperative retention, patients who are unable to discontinue anticoagulation therapy, those requesting local anesthetic, young women desiring future vaginal delivery, those patients who are unable to restrict physical activity for a formal postoperative recovery, those who have mild, persistent SUI after a previous antiincontinence surgery, and those with very mild symptoms.

Administration of the bulking agent is generally performed with a needle passed transurethrally through cystoscope into the submucosa of the proximal urethra or bladder neck. Different locations are selected for implantation (e.g., 2, 6, and 10 o'clock or 12, 4, and 8 o'clock) to allow concentric coaptation of the urethra. Periurethral techniques have also been described in which the needles are passed lateral to the urethral meatus and urethroscopy assists in localizing the injection to the proximal urethra or bladder neck. Many patients can tolerate local anesthesia with 2% viscous lidocaine jelly injected into the urethra.

Several agents have come in and out of use over the years primarily because the ideal bulking agent does not yet exist. This ideal agent would be nonimmunogenic, permanent, nonmigratory, nonerosive, noninflammatory, easily stored, easily injected, and have a high safety profile and no long-term side effects. Currently available agents include: Macroplastique (nonbiodegradable silicone hydrogel), Durasphere (carbon-coated zirconium beads), Coaptite (calcium hydroxyapatite gel), and Bulkamid (polyacrylamide hydrogel). Collagen is no longer available for use.

Most clinical studies report short-term efficacy of up to 75% in women with a substantial decrement after one year. Complications of bulking include dysuria, hematuria, periurethral abscess, urinary retention, product migration, extrusion, and urethral prolapse. The results in men have not been optimal, especially in cases of postradical prostatectomy incontinence.

f. **Retropubic suspension in the woman with or without prolapse repair**

The exact pathophysiology of SUI is unknown; however, loss of normal anatomic support of the urethrea and bladder neck and ISD are both believed to be factors.

Retropubic procedures restore the position of the bladder neck and proximal urethra to the retropubic space and are generally recommended in the setting of urethral hypermobility with the descent of the bladder neck and urethra out of the retropubic space and into the vagina with increases in IAP. Repositioning and securing the bladder neck and proximal urethra was thought to allow equal pressure transmission to the bladder and urethra during increases in IAP promoting continence. In addition, it is felt that the contraction of pelvic floor muscles to create urethral compression is more effective in the setting of a well-supported and suspended bladder neck and urethra.

The **Burch colposuspension** is the most common of the retropubic procedures and involves elevation of the anterior vaginal wall and paravesical tissue toward the iliopectineal line of the pelvis. It generally utilizes two to four sutures on either side of the urethra. A **Marshall-Marchetti-Krantz (MMK)** procedure suspends the bladder neck to the periosteum of the symphysis pubis. A **vagino-obturator shelf (VOS)** anchors the vagina to the internal obturator fascia and is essentially a combination of the Burch procedure and a paravaginal defect repair, a procedure aimed at restoration of pelvic fascial attachments of the vagina to the lateral pelvic sidewall. A minimally invasive laparoscopic approach to retropubic suspension has produced similar short-term success as the open repair, but long-term data is lacking.

g. **Sling procedures**

Ed McGuire deserves credit for popularizing the sling procedure and, more importantly, concepts that relate to its utilization. McGuire was among the first to conceptualize, in logical fashion, the fact that there was a category of women who leaked with effort who were not well repaired by standard suspension procedures. These were patients who had poor sphincter function, irrespective of mobility, and whose urethral function at that time could be semiquantitated only with the urethral pressure profile. He later developed the concept of VLPP to better quantitate sphincteric resistance in patients with stress incontinence. The noncircumferential compression afforded by the sling provides treatment for patients with poor urethral closure function and poor urethral smooth muscle function. Although originally described through a retropubic approach, these are done most commonly through a vaginal approach today. Initially, the use of the sling procedure was restricted to patients who satisfied the definition of intrinsic sphincter dysfunction and who did not have stress incontinence associated with urethral hypermobility. However, **as individuals have come to believe that stress incontinence due to hypermobility and intrinsic sphincter dysfunction were but two ends of the spectrum and that the great majority of individuals had some combination of the two, the sling procedure became, for some, a logical choice for the correction of stress incontinence of all types.** The sling provides an adequate suburethral supporting layer (see prior description of the hammock hypothesis) and thus corrects hypermobility-related incontinence and ISD. The sling itself can be autologous fascia (rectus or fascia lata), and recently a variety of other materials (cadaveric fascia, dura, synthetic materials) have been used, some with success and some with problems.

h. **Synthetic midurethral slings**

Midurethral synthetic slings, otherwise known as *tension-free vaginal tape procedures*, were born from the integral theory proposed by Petros and Ulmsten. This theory postulates that damage to the pubourethral ligaments and weakening of the pubococcygeal muscles impairs midurethral function and anterior urethral wall support, thus resulting in UI. Damage and weakening can be the result of pelvic surgery, parturition, aging, or hormonal manipulation. **This minimally invasive approach to stress incontinence surgery utilizes synthetic monofilament, polypropylene mesh with optimum porosity to allow fibrous ingrowth and inflammatory cell migration to support the midurethra.** The procedure can be performed on an outpatient basis under local, regional, or general anesthesia. Several “kits” are available utilizing slightly different insertion needles or trocars to facilitate passage of the mesh from the vaginal space to either the retropubic or obturator space. The mesh is placed at the level of the midurethra using a midline vaginal incision. Tension-free placement is insured by placing a hemostat between the urethra and mesh prior to securing the mesh in place. Careful cystoscopy is recommended in all sling-placement procedures to rule out inadvertent injury to the bladder or urethra. **Success rates range widely depending on the definition of success used but are generally felt to be 81% to 90% at greater than 3 years.** Complication rates are generally low, and these range from bladder injury to mesh erosion to de novo urgency symptoms.

i. **The advantage of autologous tissue is complete biocompatibility with extremely rare urethral erosion. The disadvantage is the increased operative time to harvest the tissue, increased postoperative pain, and potential seromas or hematomas at the harvest site.**

Rectus fascia is harvested through a Pfannenstiel incision which allows easy attainment of a 1.5 cm by 8 cm piece of fascia. Fascia lata is also a suitable material for a pubovaginal sling and can be harvested through a skin incision over the iliotibial tract. Sutures are placed on each end of the harvested sling. The sling is placed through a vaginal incision in the location of the proximal urethra or bladder neck. The retropubic space is entered bluntly to allow finger guidance of a ligature carrier from the suprapubic space to the vaginal incision. The ligature carrier allows passage of the sutures on the end of the sling through the retropubic space. Variable degrees of sling tension are possible with this approach ranging from no tension to compression. Applying the correct amount of tension is the “art” of this surgery and requires an individualized approach to each patient and surgeon experience. Cure rates from this surgery range from 67% to 97% with high patient satisfaction rates.

j. **Bladder outlet reconstruction**

This is primarily a historical treatment in adults. Reconstruction of the bladder outlet is one possible method of restoring sphincteric incontinence in patients with ISD. This technique was introduced by Young in 1907, and was subsequently modified by Dees, Leadbetter, and Tanagho. Procedures utilizing the Young-Dees principle involve construction of a neourethra from the posterior surface of the bladder wall and trigone. In the male, the prostatic urethra affords additional substance for closure and increase in outlet resistance. The Leadbetter modification involves proximal reimplantation of the ureters to allow more extensive tubularization of the trigone. Tanagho described a procedure based on a similar concept, but using the anterior bladder neck to create a functioning neourethral sphincter. "Success rates" of between 60% and 70% were reported, but it is difficult to know what success means and what the real long-term success rates are.

k. **Artificial urinary sphincter**

Control of sphincteric UI with implantable prosthetics has evolved rapidly over the last 30 years. Clearly, the most significant contribution was the introduction by F. Brantley Scott and coworkers of a totally implantable artificial sphincter mechanism that could be used in adults and children of both genders. This was originally introduced in the early 1970s. The end result of the biomechanical evolution of this device currently is most frequently utilized for postprostatectomy incontinence, but use of the device has been championed by various clinicians for refractory sphincteric incontinence of virtually every etiology, assuming bladder storage is or can be converted to normal. The sphincter consists of an inflatable cuff that fits around the urethra (generally) or the bladder neck, a reservoir that generally is placed under the rectus muscle, and an inflate/deflate pump or bulb that transfers fluid from the cuff to the reservoir, allowing refilling of the cuff from the reservoir over a 3- to 4-minute period. The pump is placed in the scrotum or the labia. High success rates have been achieved by experienced surgeons. The incidence of mechanical malfunction and infection, although it was initially high, is quite low in contemporary series with the latest iteration.

l. **Male perineal sling**

For the treatment of male SUI, most often after radical prostatectomy, the male perineal sling has emerged as a viable patient option. The male perineal sling is a minimally invasive surgical technique that involves the placement of a compressive sling at the level of the bulbar urethra. This is generally anchored to the descending pubic rami, most often with bone screws. With this technique, there is nothing for the patient to manipulate. Because of the minimal dissection that is needed, one theoretical benefit is less chance for any urethral complications. It also appears to be safe in those who have a previous artificial urinary sphincter or radiation therapy. Success rates have varied depending on the end point. Few complications have been noted, including perineal/scrotal numbness (usually self-limited), infection, and bone screw dislodgment. A review of the literature on male perineal slings suggests that this is another effective option in the treatment of male SUI; however, it may be best reserved for those men with only mild to moderate incontinence.

m. **Closure of the bladder outlet**

This is generally an end-stage procedure suitable for an individual whose outlet is totally incompetent and uncorrectable by medical or conventional surgical means. It is also sometimes used in individuals who can be put into retention but who cannot catheterize themselves per urethra. In this latter condition and in the circumstance of an incompetent urethra in an individual with adequate hand control who desires to be dry, a continent catheterizable abdominal stoma can be created. Augmentation cystoplasty can be carried out at the same time. For individuals lacking adequate hand control or the cognitive facilities necessary for intermittent catheterization or who simply do not want to carry out catheterization, a chimney-type conduit of bowel is created emanating from the bladder with an abdominal stoma that drains into an appliance.

3. **Circumventing the problem**

**Antidiuretic hormonelike agents** have been mentioned under the category of pharmacologic therapy. Another “trick” utilized in an individual with significant nocturia is to try to adjust diuretic dosage, utilizing a **short-acting diuretic** some time in the afternoon, the object being to reduce the amount of fluid mobilized after the individual goes to bed.

Popularization of **intermittent catheterization** as a treatment modality has made possible many of the other therapeutic options for the treatment of voiding dysfunction that are now commonplace. Originally introduced by Guttman in the treatment of SCI patients as a method of reducing UTI, credit needs to go to Jack Lapides for advocating and popularizing the use of CIC for all types of voiding dysfunction in which such circumvention of storage or emptying failure is necessary. The details (types of catheters, intervals, cleansing and sterilization regimens, and prophylaxis or not) are specific to practitioner and institution.

**Indwelling urethral or suprapubic catheters** are generally used for short-term bladder drainage. The use of a small-bore catheter for a short time, does not, with proper care, seem to adversely affect the ultimate outcome. Occasionally, more often in female patients, an indwelling catheter is a last-resort type of therapy for long-term bladder drainage. A contracted fibrotic bladder may be the ultimate result; bladder calculi may form on the catheter; urethral complications in the female may include urethral dilation because of the temptation to replace each catheter with a larger diameter one to prevent leakage around the catheter consequent to bladder spasm. A suprapubic catheter does not obviate urethral leakage and does not provide better drainage in patients with sphincteric incontinence. It may be easier to wear, but it is more difficult to replace. There is still some controversy as to whether long-term indwelling catheterization, especially in the female, in the neurologically challenged population, is associated with a poorer outcome with respect to either significant upper and lower tract complications or quality of life. It must be kept in mind that development of carcinoma of the bladder in patients with long-term indwelling catheter drainage is possible, and so adequate monitoring of such patients is necessary.

**External collecting devices** are useful only in the male. A suitable external collecting device has not yet been devised for the female. Care must be taken in individuals with sensory impairment to avoid necrosis of the penis because of an inappropriately tightly fitting device. It is difficult to know whether to label **pads** and **absorbent products** as a treatment for refractory incontinence or as a convenient "bail-out." They are used for both. Approximately $2 billion is currently spent in the United States yearly for pads and absorbent products.

**Urinary diversion** is a last resort for these patients and is in a category known as "desperate measures." The diversion can utilize the patient's own bladder for storage if the outlet is competent or closure can be accomplished, or a continent catheterizable reservoir can be constructed totally of bowel. Sometimes, the tried-and-true intestinal conduit (Bricker or bilateral ureteroileostomy) will represent, all things considered, the best choice for an individual patient. The usually listed standard indications for supravesical urinary diversion include (1) progressive hydronephrosis or intractable upper tract dilation (which may be due to obstruction at the ureterovesical junction or to VUR that does not respond to conservative measures), (2) recurrent episodes of sepsis, and (3) intractable filling and storage or emptying failure when CIC is impossible.

## THERAPY TO FACILITATE BLADDER EMPTYING AND VOIDING

1. **Bladder related (increasing intravesical pressure or facilitating bladder contractility)**

   ***Detrusor underactivity continues to be a major problem without a satisfactory solution.***

   a. **External compression, Valsalva**

   Such voiding is unphysiologic and is resisted by the same forces that normally resist stress incontinence. Adaptive changes (funneling) of the bladder outlet generally do not occur with external compression maneuvers of any kind. Increases in outlet resistance may actually occur. The greatest likelihood of success with this mode of therapy (although some would say it should never be used) is in the patient with an areflexic and hypotonic or atonic bladder and some defunctionalization of the outlet (smooth or striated sphincter or both). Such a patient not uncommonly has stress incontinence as well. The continued use of external compression or Valsalva maneuver implies that the intravesical pressure between attempted voidings is consistently below that associated with upper tract deterioration. This may be an erroneous assumption, and close follow-up and periodic evaluation are necessary to avoid this complication.

b. **Promotion or initiation of reflex contractions**

In most types of SCI characterized by DO, manual stimulation of certain areas within sacral and lumbar dermatomes may provoke a reflex bladder contraction. The most effective classic method of doing so is rhythmic suprapubic manual pressure. If the pressure characteristics of such induced voiding are favorable, and induced emptying can be carried out frequently enough so as to keep bladder volume and pressure below the level dangerous for upper tract deterioration, the incontinence can be "controlled," and, conceptually, this amounts to a form of timed voiding in these neurologically impaired patients. Some clinicians still believe that the establishment of a rhythmic pattern of bladder filling and emptying by maintaining a copious fluid intake and by periodically clamping and unclamping an indwelling catheter or by intermittent catheterization can "condition" or "train" the micturition reflex. This concept, in our opinion, has yet to be proven, and it may be that the prime value of such programs is to focus attention on the urinary tract and ensure an adequate fluid intake.

c. **Pharmacologic therapy**

1) **Parasympathomimetic agents**

Many acetylcholine-like drugs exist. However, only bethanechol chloride exhibits a relatively selective action on the urinary bladder and gut with little or no action at therapeutic dosages on ganglia or the cardiovascular system. It is cholinesterase resistant and causes a contraction in vitro of smooth muscle from all areas of the bladder. Although anecdotal success in rare patients with voiding dysfunction seems to occur, attempts to facilitate bladder emptying in a series of patients where bethanechol chloride was the only variable have been disappointing. In adequate doses, bethanechol chloride is capable of eliciting an increase in tension in bladder smooth muscle, as would be expected from in vitro studies, but its ability to stimulate or facilitate a physiologic bladder contraction in patients with voiding dysfunction has been unimpressive. **It is difficult to find reproducible urodynamic data that support a general recommendation for the use of bethanechol chloride in any specific category of patients.**

2) **Other pharmacologic treatments**

One could construct a "wish list" of other potential pharmacologic avenues for facilitating bladder contractility or the micturition reflex. In the cat at least (see previous discussion) there is a sympathetic reflex elicited during filling that promotes urine storage partially by exerting an α-adrenergic inhibitory effect on pelvic parasympathetic ganglionic transmission. **Alpha-adrenergic blockade,** theoretically, then could facilitate transmission through these ganglia and thereby enhance bladder contractility. Alpha-adrenergic blockers are sometimes given for the "treatment" of urinary retention, using this rationale, but whether relief of retention occurs because of the use of these agents or simply simultaneously is unknown. Because endogenous opioids have been hypothesized to exert a tonic inhibitory effect on the micturition reflex at various levels, **narcotic antagonists** offer possibilities for stimulating reflex bladder activity. This concept has never been translated into successful clinical use. **Prostaglandins** contribute to the maintenance of bladder tone and bladder contractile activity. Some subtypes cause an in vitro and in vivo bladder contractile response and some cause a decrease in urethral smooth muscle tone. Intravesical prostaglandin use has been reported to facilitate voiding in postsurgical patients. A number of conflicting positive and negative reports exist, and double-blind placebo studies are obviously necessary to settle this controversy.

d. **Electrical stimulation**

Stimulation directly to the bladder or spinal cord originated in the 1940s but met with failure. Fibrosis related to the electrodes, bladder erosion, electrode malfunction, or other equipment malfunction was common. The spread of current to other pelvic structures with stimulus thresholds lower than that of the bladder resulted in undesirable stimulation of a number of bodily processes.

Stimulation to the nerve roots has been pursued for the last 40 years, initially by Brindley, Tanagho, and Schmidt for the treatment of voiding dysfunction. Anterior sacral root stimulation, in combination with dorsal rhizotomy or dorsal root ganglionectomy, has become a practicality and a reality, especially in patients with SCI. Prerequisites for such usage are (1) intact neural pathways between the sacral cord nuclei of the pelvic nerve and the bladder and (2) a bladder that is capable of contracting. The champions of these techniques deserve much credit for pursuing and developing their ideas over the years, in the face of much negative opinion as to the possibility of their ultimate success. Although these techniques are still in a phase of evolution, they are currently practical and hold much promise for the future.

Intravesical electrostimulation is an old technique that has been resurrected with some very interesting and promising results. The mechanism of action is totally unknown, and it is similar to neuromodulation in two respects: the vague way in which it is defined and the definition of its mechanism of action. Patients with incomplete central or peripheral nerve lesions and with at least some neural pathways between the bladder and cerebral centers are candidates for this technique. One conceptualization of the mechanism of efficacy invokes the involvement of an artificial activation of the micturition reflex, with repeated activation producing an “upgrade” of the micturition reflex.

e. **Reduction cystoplasty**

The problem of myogenic decompensation has suggested surgical reduction to some investigators because the chronic overstretching affects mainly the upper free part of the bladder, and the nerve and vessel supply enter primarily from below. Thus resection of the dome (or doubling this over) does not influence the function of the spared bladder base and lower bladder body. This technique would seem to be most effective when the detrusor was underactive rather than acontractile, and measures to decrease outlet resistance might be required in addition to achieve adequate emptying. Anecdotal success stories aside, the risk-benefit ratio of this procedure has not been established.

2. **Outlet related** (**decreasing outlet resistance**)
   a. **At a site of anatomic obstruction**

These measures are all discussed in the chapters on benign prostatic hyperplasia (Chapter 15) and urethral stricture disease (Chapter 11).

b. **At the level of the smooth sphincter**

1) **Pharmacologic therapy**

Bob Krane and Carl Olsson promoted the concept of a physiologic internal sphincter partially controlled by tonic sympathetic stimulation of contractile α-adrenergic receptors in the smooth musculature of the bladder neck and proximal urethra. Further, they hypothesized that some obstructions at this level are a result of inadequate opening of the bladder neck and/or inadequate decrease in resistance in the area of the proximal urethra. They also theorized and presented evidence that **α-adrenergic blockade** could be useful in promoting bladder emptying in such a patient with an adequate detrusor contraction but without anatomic obstruction or detrusor-striated sphincter dyssynergia. Although most would agree that α-adrenergic blocking agents exert at least some of their favorable effects on voiding dysfunction by affecting the smooth muscle of the bladder neck and proximal urethra, some other information in the literature suggests that they may affect striated sphincter tone as well. These agents are also used to treat obstruction due to BPH by lowering prostatic smooth muscle "tone" and may have some secondary effects on bladder contractility in these patients as well, probably mediated through different receptor subtypes or at the level of the CNS.

**Phenoxybenzamine** was the α-AR antagonist originally used for the treatment of voiding dysfunction. Side effects affect approximately 30% of patients and include orthostatic hypotension, reflex tachycardia, nasal congestion, diarrhea, miosis, sedation, nausea, and vomiting (secondary to local irritation).

**Prazosin** was the first potent selective α-AR antagonist used to lower outlet resistance. The potential side effects of prazosin are consequent to its α-AR blockade. Occasionally, there occurs a "first-dose phenomenon," a symptom complex of faintness, dizziness, palpitation, and, infrequently, syncope, thought to be caused by acute postural hypotension.

**Terazosin** and **doxazosin** are two highly selective postsynaptic $\alpha_1$-AR antagonists. They are readily absorbed with high bioavailability and a long plasma half-life, enabling their activity to be maintained over 24 hours after a single oral dose. Both of these agents have been evaluated with respect to their efficacy in patients with LUT symptoms and decreased flow rates presumed secondary to BPH. Their efficacy in decreasing symptoms and raising flow rates has been shown to be superior to placebo. Their safety profiles have been well documented as a result of their widespread use over several years for the treatment of hypertension. Side effects are related to peripheral vasodilatation (postural hypotension), and both drugs have to be started at a low dose and titrated to obtain an optimal balance between efficacy and tolerability. Dizziness and weakness are sometimes observed, and these are presumed secondary to CNS actions. These drugs are sometimes useful for the treatment of individuals with both outlet obstruction and hypertension.

**Alfuzosin, tamsulosin, and silodosin,** all highly selective $\alpha_1$-AR blockers, are marketed solely for the treatment of BPH. Reports suggest preferential action on prostatic rather than vascular smooth muscle. Marketing claims aside, whether there is any clinically relevant difference in the efficacy and side effect profiles of these individual agents and between them and the nonuroselective alpha-blockers remains a topic of controversy. These are discussed in more detail in Chapter 15.

2) **Transurethral resection or incision of the bladder neck/smooth sphincter**

The prime indication for transurethral resection or incision of the bladder neck is the demonstration of true obstruction at the bladder neck by combining urodynamic studies with either fluoroscopic demonstration of failure of opening of the smooth sphincter area or a micturitional profile showing that the pressure falls off sharply at some point between the bladder neck and the area of the striated sphincter. Bladder neck or smooth sphincter dyssynergia has been previously discussed, and it is this entity (occurring almost exclusively in males) that is the most common indication for the current performance of transurethral incision or resection of the bladder neck. The preferred technique at this time in the male is incision of the bladder neck at the 4-5 o'clock and/or 7-8 o'clock position, with a single full-thickness incision extending from the bladder base down to the level of the verumontanum. Most clinicians would place the incidence of retrograde or diminished ejaculation somewhere between the reported incidences of 10% and 80%.

3) **Y-V plasty of the bladder neck**

This is recommended or suggested only when a bladder neck resection or incision is desired and an open surgical procedure is simultaneously required to correct a concomitant disorder. This is rarely carried out.

c. **At the level of the striated sphincter**

1) **Behavioral therapy with or without biofeedback**

Behavioral therapy in this case is used to facilitate emptying in an individual with occult voiding dysfunction (characteristics of striated sphincter dyssynergia, but neurologically normal). A urodynamic display of striated sphincter activity can facilitate clinical improvement in a strongly motivated patient capable of understanding the instructions of biofeedback-assisted therapy, in this case pelvic floor relaxation.

2) **Pharmacologic therapy**

There is, unfortunately, no class of pharmacologic agents that selectively relaxes the striated musculature of the pelvic floor. Three different types of drugs have been used to treat voiding dysfunction secondary to outlet obstruction at the level of the striated sphincter: (1) **benzodiazepines,** (2) **baclofen,** and (3) **dantrolene,** all of which have been characterized under the general heading of antispasticity drugs. Baclofen and the benzodiazepines exert their actions predominantly within the CNS, whereas dantrolene acts directly on skeletal muscle. Unfortunately, there is no completely satisfactory oral form of therapy for alleviation of skeletal muscle spasticity. Although these drugs are capable of providing variable relief of spasticity in some circumstances, their efficacy is far from complete, and this, along with troublesome muscle weakness, adverse effects on gait, and a variety of other side effects, minimizes their overall usefulness. Alpha-adrenergic blocking agents have also been hypothesized to exert an inhibitory effect on the striated sphincter, and this may be especially pronounced in those cases in which neuroplasticity with altered innervation of this area has occurred. Finally, **botulinum toxin** has been injected directly into the striated sphincter to reduce its tone, and the results have been impressive (see prior section on BTX).

3) **Surgical sphincterotomy**

The primary indication for this procedure is detrusor-striated sphincter dyssynergia in a male patient when other types of management have been unsuccessful or are not possible. A substantial improvement in bladder emptying occurs in 70% to 90% of cases. Upper tract deterioration is rare following successful sphincterotomy; VUR, if present preoperatively, often disappears because of decreased bladder pressures and a reduced incidence of infection in a catheter-free patient with a low residual-urine volume. An external collecting device is generally worn postoperatively, although total dripping incontinence or severe stress incontinence is unusual unless the proximal sphincter mechanism (the bladder neck and proximal urethra) has been compromised — by prior surgical therapy, the neurologic lesion itself, or as a secondary effect of the striated sphincter dyssynergia (presumably a hydraulic effect on the bladder neck itself). The 12 o'clock sphincterotomy remains the procedure of choice for a number of reasons. The anatomy of the striated sphincter is such that its main bulk is anteromedial. The blood supply is primarily lateral, and thus there is less chance of significant hemorrhage with a 12 o'clock incision. There is some disagreement about the rate of postoperative ED in those individuals who preoperatively have erections. Estimates utilizing the 3 o'clock and 9 o'clock technique vary from 5% to 30%, but whatever the true figure is, it is clear that most would agree that this complication is far less common (approximately 5%) with incision in the anteromedial position. Other complications may include significant hemorrhage and urinary extravasation. Failure to attain satisfactory bladder emptying following external sphincterotomy may be due to inadequate or poorly sustained bladder contractility, a poorly done sphincterotomy, or persistent obstruction at the level of the bladder neck from unrecognized coexistent smooth sphincter dyssynergia. In these latter patients, bladder neck incisions, as described previously, may facilitate bladder emptying. Botulinum toxin A injection into the sphincter can achieve similar benefit with fewer complications.

4) **Urethral overdilation**

   Overdilation to 40 to 50 French in female patients can achieve the same objective as external sphincterotomy but is rarely used. If incontinence results, there is no suitable external collection device for women. It is sometimes used in young boys, when sphincterotomy is contemplated, and a similar stretching of the posterior urethra can be accomplished through a perineal urethrostomy. Observations indicate that, in myelomeningocele patients treated by this method, compliance can be improved by decreasing the outlet resistance.

5) **Urethral stent**

   Permanent urethral stents to bypass the sphincter area have been utilized. There is little question that a significant decrease in detrusor leak pressure and residual urine volume occurs. The questions are long-term efficacy, ease of removal and replacement when required, and the true incidence of the development of BOO.

6) **Pudendal nerve interruption**

   This procedure, first described in the late 1890s, is seldom if ever used today because of the potential of undesirable effects consequent to even a unilateral nerve section (impotence, and fecal and stress incontinence).

**Additional content, including Self-Assessment Questions, Suggested Readings, as well as Algorithms for the Management of Urinary Incontinence, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Regardless of differences regarding physiologic and pharmacologic details, what would most experts agree are the requirements for normal bladder filling/storage and emptying/voiding? Discuss the main points relating to the anatomy, neurophysiology, and neuropharmacology of each of these factors.*
2. *Characterize the most common types of voiding dysfunction seen with the following neurologic injury(ies) and disease(s) in terms of sensation, bladder activity, smooth sphincter activity, and striated sphincter activity: (1) cerebrovascular accident, (2) Parkinson disease, (3) multiple sclerosis, (4) suprasacral spinal cord injury, (5) sacral spinal cord injury, (6) radical pelvic surgery, and (7) diabetes.*
3. *Describe and discuss the use of pressure flow urodynamic studies and video urodynamic studies.*
4. *Discuss the possibilities and practicalities of pharmacologic therapy and neuromodulation for (1) detrusor overactivity (DO), (2) decreased outlet resistance, (3) increased outlet resistance and (4) decreased bladder contractility and detrusor underactivity.*
5. *Discuss the pathophysiology and surgical options for treating sphincteric incontinence in adult men and women.*

### SUGGESTED READINGS

1. Abrams P, Cardozo L, Khoury S, et al, editors: *Incontinence*, ed 5 Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.

   **Chapters:**

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   2. Cell Biology. Fry CH, Chacko S, de Wachter S, et al, pp 109–178.
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   4. Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse. Koelbl H, Igawa T, Salvatore S, et al, pp 261–360.
   5. A) Initial Assessment of Urinary Incontinence in Adult Male and Female Patients. Staskin D, Kelleher C, Bosch R, et al, pp 361–428.
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   8. Pharmacological Treatment of Urinary Incontinence. Andersson KE, Chapple CR, Cardozo L, et al, pp 623–728.
   10. Neurologic Urinary and Faecal Incontinence. Drake MJ, Apostolidis A, Emmanuel A, et al, pp 827–1000.

12. Adult Conservative Management. Moore K, Dumoulin C, Bradley C, et al, pp 1101–1228.
13. Surgical Treatment of Urinary Incontinence in Men. Herschorn S, Bruschini H, Comiter C, et al, pp 1229–1306.
14. Surgery for Urinary Incontinence in Women. Dmochowski R, Athanasiou S, Reid F, et al, pp 1307–1376.
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3. Andersson KE, Arner A: Urinary bladder contraction and relaxation: physiology and pathophysiology, *Physiol Rev* 84:935–988, 2004.
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62. Urodynamic and Video-Urodynamic Evaluation of the Lower Urinary Tract, Nitti VW, pp 1847–1870.
63. Urinary Incontinence and Pelvic Prolapse: Epidemiology and Pathophysiology. Chapple CR, Milsom I, pp 1871–1895.
64. Evaluation of Patients with Urinary Incontinence and Pelvic Prolapse. Kobashi KC, pp 1896–1908.
65. Neuromuscular Dysfunction of the Lower Urinary Tract. Wein AJ, Dmochowski RR, pp 1909–1946.
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67. Nocturia. Drake M, pp 1958–1966.
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69. Conservative Management of Urinary Incontinence: Behavioral and Pelvic Floor Therapy, Urethral and Pelvic Devices. Payne CK, pp 2003–2025.
70. Electrical Stimulation and Neuromodulation in Storage and Emptying Failure. Vasavada SP, Rackley RR, pp 2026–2046.
71. Retropubic Suspension Surgery for Incontinence in Women. Chapple CR, pp 2047–2068.

TABLE 14-e1 **Management of Urinary Incontinence in Men**
A. Initial Management

**1. Initial assessment should identify:**

***"Complicated" incontinence group***

Those with pain or with hematuria, recurrent infections, suspected or proven poor bladder emptying (e.g., due to bladder outlet obstruction [BOO]), or incontinence following pelvic irradiation or radical surgery are recommended for ***specialized management.***

***Poor bladder emptying*** may be suspected from symptoms and physical examination or if imaging has been performed by x-ray or ultrasound (US) after voiding.

***Four other main groups*** of men should be identified by initial assessment as being suitable fo***r initial management.***

- Those with postmicturition dribble alone
- Those with overactive bladder (OAB) symptoms: Urgency with or without urgency incontinence, together with frequency and nocturia
- Those with stress incontinence (most often postprostatectomy)
- Those with mixed urgency and stress incontinence (most often postprostatectomy)

***2. Management***

For men with ***postmicturition dribble,*** this requires no assessment and can usually be treated by teaching the man how to do a strong pelvic-floor muscle contraction after voiding or manual compression of the bulbous urethra directly after micturition. (Grade B)

For men with **stress, urgency***, or* **mixed** urgency and stress incontinence, initial treatment should include appropriate lifestyle advice, pelvic-floor muscle training, scheduled voiding regimens, behavioral therapies, and medication. In particular:

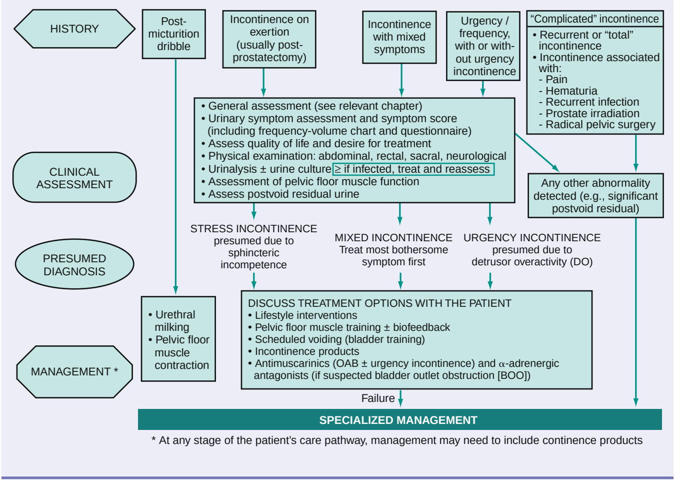
- Lifestyle interventions (Grade D)
- Supervised pelvic-floor muscle training for men with postradical prostatectomy stress urinary incontinence (SUI) (Grade B)
- Scheduled voiding regimens for OAB (Grade C)
- Antimuscarinic drugs for OAB symptoms with or without urgency incontinence (Grade B) if the patient has no evidence of significant postvoid residual urine
- Alpha-adrenergic antagonists (α-blockers) can be added if it is thought that there may also be BOO. (Grade C)

***Should initial treatment be unsuccessful*** after a reasonable period of time (for example, 8-12 weeks), ***specialist advice*** is highly recommended.

Clinicians are likely to wish to treat the ***most bothersome symptom*** first in men with symptoms of ***mixed*** incontinence.

(*Continued*)

TABLE 14-e1 **Management of Urinary Incontinence in Men—Cont'd**


Initial Management of Urinary Incontinence In Men
HISTORY
CLINICAL ASSESSMENT
PRESUMED DIAGNOSIS
MANAGEMENT *
Post-micturition dribble
Incontinence on exertion (usually post-prostatectomy)
Incontinence with mixed symptoms
Urgency / frequency, with or without urgency incontinence
"Complicated" incontinence
• Recurrent or "total" incontinence
• Incontinence associated with:
- Pain
- Hematuria
- Recurrent infection
- Prostate irradiation
- Radical pelvic surgery
• General assessment (see relevant chapter)
• Urinary symptom assessment and symptom score (including frequency-volume chart and questionnaire)
• Assess quality of life and desire for treatment
• Physical examination: abdominal, rectal, sacral, neurological
• Urinalysis ± urine culture ≥ if infected, treat and reassess
• Assessment of pelvic floor muscle function
• Assess postvoid residual urine
Any other abnormality detected (e.g., significant postvoid residual)
STRESS INCONTINENCE presumed due to sphincteric incompetence
MIXED INCONTINENCE Treat most bothersome symptom first
URGENCY INCONTINENCE presumed due to detrusor overactivity (DO)
• Urethral milking
• Pelvic floor muscle contraction
DISCUSS TREATMENT OPTIONS WITH THE PATIENT
• Lifestyle interventions
• Pelvic floor muscle training ± biofeedback
• Scheduled voiding (bladder training)
• Incontinence products
• Antimuscarinics (OAB ± urgency incontinence) and α-adrenergic antagonists (if suspected bladder outlet obstruction [BOO])
Failure
SPECIALIZED MANAGEMENT
* At any stage of the patient's care pathway, management may need to include continence products

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e2 **Management of Urinary Incontinence in Men**
B. Specialized Management

The specialist may first **reinstitute initial management** if it is felt that previous therapy had been inadequate.

**1. Assessment**

Patients with ***"complicated" incontinence*** referred directly to specialized management are likely to require ***additional testing*** such as cytology, cystourethroscopy, and urinary tract imaging.

***If these tests prove normal,*** then those individuals can be treated for incontinence by the initial or specialized management options as appropriate.

***If symptoms*** suggestive of detrusor overactivity (DO) or sphincter incompetence ***persist,*** then ***urodynamic*** studies are advisable in order to arrive at a precise diagnosis prior to invasive treatment.

**2. Treatment**

**When basic management has failed** and if the patient's incontinence markedly disrupts his quality of life, then ***invasive therapies*** should be considered.

***For sphincter incompetence,*** the recommended option is the artificial urinary sphincter (Grade B). Other options, such as a male sling, may be considered (Grade C).

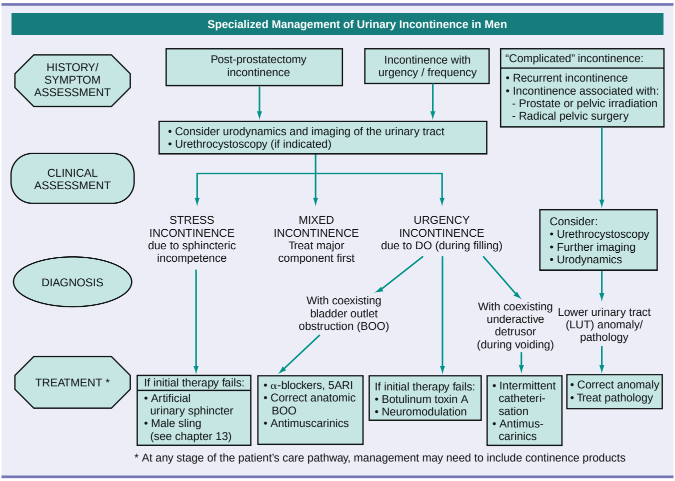
***For idiopathic DO***, (with intractable overactive bladder [OAB] symptoms) the recommended therapies are botulinum toxin A (Grade B), neuromodulation (Grade C), and bladder augmentation (Grade C).*

When incontinence has been shown to be associated with ***poor bladder emptying*** and ***detrusor underactivity,*** it is recommended that effective means are used to ensure bladder emptying (e.g., intermittent catheterization) (Grade B/C).

***If incontinence is associated with bladder outlet obstruction*** (BOO), then consideration should be given to surgical treatment to relieve obstruction (Grade B). Alpha-blockers and/or 5-α- reductase inhibitors would be an optional treatment (Grade C). There is increased evidence for the safety of antimuscarinics for OAB symptoms in men, chiefly in combination with an α-blocker (Grade B).

(*Continued*)

TABLE 14-e2 **Management of Urinary Incontinence in Men—Cont'd**


Specialized Management of Urinary Incontinence in Men
HISTORY/ SYMPTOM ASSESSMENT
CLINICAL ASSESSMENT
DIAGNOSIS
TREATMENT *
Post-prostatectomy incontinence
Incontinence with urgency / frequency
"Complicated" incontinence:
• Recurrent incontinence
• Incontinence associated with:
- Prostate or pelvic irradiation
- Radical pelvic surgery
• Consider urodynamics and imaging of the urinary tract
• Urethrocystoscopy (if indicated)
STRESS INCONTINENCE due to sphincteric incompetence
MIXED INCONTINENCE Treat major component first
URGENCY INCONTINENCE due to DO (during filling)
Consider:
• Urethrocystoscopy
• Further imaging
• Urodynamics
With coexisting bladder outlet obstruction (BOO)
With coexisting underactive detrusor (during voiding)
Lower urinary tract (LUT) anomaly/ pathology
If initial therapy fails:
• Artificial urinary sphincter
• Male sling (see chapter 13)
• α-blockers, 5ARI
• Correct anatomic BOO
• Antimuscarinics
If initial therapy fails:
• Botulinum toxin A
• Neuromodulation
• Intermittent catheterisation
• Antimuscarinics
• Correct anomaly
• Treat pathology
* At any stage of the patient's care pathway, management may need to include continence products

** Note: At the time of writing, botulinum toxin for idiopathic DO is being used "off-label."*

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e3 **Management of Urinary Incontinence in Women**
A. Initial Management

**1. Initial assessment should identify:**

***"Complicated" incontinence group***

Those with pain or hematuria, recurrent infections, suspected or proven voiding problems, significant pelvic organ prolapse; or who have persistent incontinence or recurrent incontinence after pelvic irradiation, radical pelvic surgery, or previous incontinence surgery; or who have a suspected fistula should be referred to a specialist.

***Three other main groups*** of patients should be identified by initial assessment.

- Women with ***stress incontinence*** on physical activity
- Women with ***urgency, frequency*** with or without urgency incontinence
- Those women with ***mixed*** urgency and stress incontinence

Abdominal, pelvic, and perineal examinations should be a routine part of a physical examination. Women should be asked to perform a "stress test" (cough and strain to detect leakage likely to be due to sphincter incompetence). Any pelvic organ prolapse or urogenital atrophy should be assessed. Vaginal or rectal examination allows the assessment of voluntary pelvic floor muscle function, an important step prior to the teaching of pelvic-floor muscle training.

**2. Treatment**

For women with ***stress, urgency, or mixed*** urinary incontinence, initial treatment should include appropriate lifestyle advice, pelvic-floor muscle training (PFMT), scheduled voiding regimens, behavioral therapies, and medication. In particular:

- ***Advice*** on caffeine reduction (Grade B) and weight reduction (Grade A)
- ***Supervised PFMT*** (Grade A), ***supervised vaginal cones training*** for women with stress incontinence (Grade B)
- ***Supervised bladder training*** (Grade A) for overactive bladder (OAB)
- ***If estrogen deficiency*** and/or urinary tract infection (*UTI*) is found, the patient should be treated at initial assessment and then reassessed after a suitable interval using vaginal estrogens (Grade B).
- ***Antimuscarinics*** for OAB symptoms with or without urgency incontinence (Grade A); duloxetine* may be considered for stress urinary incontinence (SUI) (Grade B)

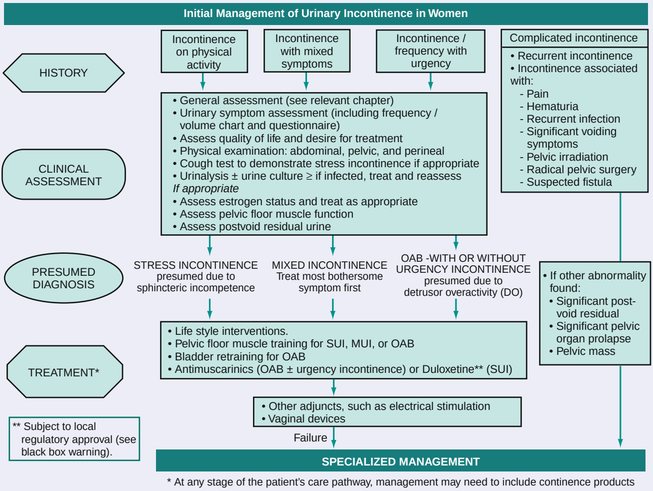
(*Continued*)

TABLE 14-e3 **Management of Urinary Incontinence in Women—Cont'd**

PFMT should be based on sound muscle-training principles, such as specificity, overload progression, correct contraction confirmed prior to training, and use of the Knack maneuver for 12 weeks before reassessment and possible specialist referral.

Clinicians are likely to wish to treat the ***most bothersome symptom first*** in women with symptoms of mixed incontinence (Grade C).

Some women with significant ***pelvic organ prolapse*** can be treated by vaginal devices that treat both incontinence and prolapse (incontinence rings and dishes).


Initial Management of Urinary Incontinence in Women
HISTORY
CLINICAL ASSESSMENT
PRESUMED DIAGNOSIS
TREATMENT*
Incontinence on physical activity
Incontinence with mixed symptoms
Incontinence / frequency with urgency
Complicated incontinence
• Recurrent incontinence
• Incontinence associated with:
- Pain
- Hematuria
- Recurrent infection
- Significant voiding symptoms
- Pelvic irradiation
- Radical pelvic surgery
- Suspected fistula
• General assessment (see relevant chapter)
• Urinary symptom assessment (including frequency / volume chart and questionnaire)
• Assess quality of life and desire for treatment
• Physical examination: abdominal, pelvic, and perineal
• Cough test to demonstrate stress incontinence if appropriate
• Urinalysis ± urine culture ≥ if infected, treat and reassess
If appropriate
• Assess estrogen status and treat as appropriate
• Assess pelvic floor muscle function
• Assess postvoid residual urine
STRESS INCONTINENCE presumed due to sphincteric incompetence
MIXED INCONTINENCE Treat most bothersome symptom first
OAB -WITH OR WITHOUT URGENCY INCONTINENCE presumed due to detrusor overactivity (DO)
• If other abnormality found:
• Significant post-void residual
• Significant pelvic organ prolapse
• Pelvic mass
• Life style interventions.
• Pelvic floor muscle training for SUI, MUI, or OAB
• Bladder retraining for OAB
• Antimuscarinics (OAB ± urgency incontinence) or Duloxetine** (SUI)
• Other adjuncts, such as electrical stimulation
• Vaginal devices
Failure
SPECIALIZED MANAGEMENT
** Subject to local regulatory approval (see black box warning).
* At any stage of the patient's care pathway, management may need to include continence products

* Duloxetine is not approved for use in the United States. It is approved for use in Europe for severe stress incontinence (see committee report on pharmacological management for information regarding efficacy, adverse events, and "black box" warning by the U.S. Food and Drug Administration).

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e4 **Management of Urinary Incontinence in Women**
B. Specialized Management

**1. Assessment**

Women who have "*complicated" incontinence* (see initial algorithm) may need to have additional tests, such as cytology, cystourethroscopy, or urinary tract imaging. If these tests are normal, patients should be treated for incontinence by the initial or specialized management options as appropriate.

Those women who have *failed initial management* and whose quality of life is impaired are likely to request further treatment. If initial management has been given an adequate trial, then *interventional therapy may be desirable*. Prior to intervention, *urodynamic testing* is highly recommended when the results may change management. It is used to diagnose the type of incontinence and therefore inform the management plan. Within the urodynamic investigation, urethral-function testing by urethral-pressure profile or leak-point pressure is optional.

Systematic assessment for *pelvic organ prolapse* is highly recommended, and it is suggested that the POP-Q method should be used in research studies. Women with coexisting pelvic organ prolapse should have their prolapse treated as appropriate.

**2. Treatment**

*If urodynamic stress incontinence is confirmed,* then the treatment options that are recommended for patients with *some degree of bladder-neck and urethral mobility* include the full range of nonsurgical treatments, retropubic suspension procedures (Grade A), and bladder neck/suburethral sling operations (Grade A). The *correction of symptomatic* pelvic organ prolapse may be desirable at the same time.

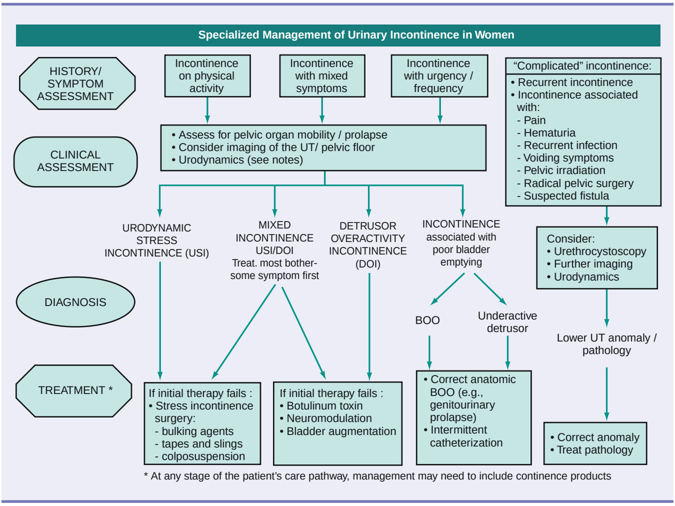
For patients with *limited bladder neck mobility,* bladder neck sling procedures (Grade A), injectable bulking agents (Grade B), and the artificial urinary sphincter (Grade B) can be considered.

Refractory *urgency incontinence* (overactive bladder [OAB]) secondary to idiopathic detrusor overactivity (DO) may be treated by botulinum toxin A (Grade C)*, neuromodulation (Grade A), or bladder augmentation (Grade C).

Those patients with *voiding dysfunction* leading to significant postvoid residual urine (e.g., > 30% of total bladder capacity) may have bladder outlet obstruction (BOO) or detrusor underactivity. Prolapse is a common cause of voiding dysfunction.

(*Continued*)

TABLE 14-e4 **Management of Urinary Incontinence in Women—Cont'd**


Specialized Management of Urinary Incontinence in Women
HISTORY/ SYMPTOM ASSESSMENT
Incontinence on physical activity
Incontinence with mixed symptoms
Incontinence with urgency / frequency
"Complicated" incontinence:
• Recurrent incontinence
• Incontinence associated with:
- Pain
- Hematuria
- Recurrent infection
- Voiding symptoms
- Pelvic irradiation
- Radical pelvic surgery
- Suspected fistula
CLINICAL ASSESSMENT
• Assess for pelvic organ mobility / prolapse
• Consider imaging of the UT/ pelvic floor
• Urodynamics (see notes)
Consider:
• Urethrocystoscopy
• Further imaging
• Urodynamics
URODYNAMIC STRESS INCONTINENCE (USI)
MIXED INCONTINENCE USI/DOI Treat. most bother-some symptom first
DETRUSOR OVERACTIVITY INCONTINENCE (DOI)
INCONTINENCE associated with poor bladder emptying
DIAGNOSIS
BOO
Underactive detrusor
Lower UT anomaly / pathology
TREATMENT *
If initial therapy fails :
• Stress incontinence surgery:
- bulking agents
- tapes and slings
- colposuspension
If initial therapy fails :
• Botulinum toxin
• Neuromodulation
• Bladder augmentation
• Correct anatomic BOO (e.g., genitourinary prolapse)
• Intermittent catheterization
• Correct anomaly
• Treat pathology
* At any stage of the patient's care pathway, management may need to include continence products

* *At the time of writing, botulinum toxin is being used "off-label" and with caution.*

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e5 **Management of Urinary Incontinence in Frail Older Men and Women**

There is no reason to suspect why interventions that have proven efficacy in the community-dwelling elderly should not also be effective in frail older people. Clinicians should, however, take due regard of the practicality, potential benefits, and dangers of employing any single intervention in this population. Frail older people do require a different approach addressing the potential role of comorbid disease, current medications (prescribed, over the counter, and/or naturopathic), and functional and cognitive impairment in urinary and fecal incontinence. The extent of the investigation and management should take into account the degree of bother to the older person and/or caregiver, the goals for care, the degree that the older person is able to undertake any intervention, and the overall prognosis and life expectancy. Effective management to meet the goals of care should be possible for most frail older people.

**I. History and Symptom Assessment**

- Active case finding for urinary and fecal incontinence should be done in all frail older people (Grade A). History should include comorbid conditions and medications that could cause or worsen incontinence. Physical examination should include a rectal examination for fecal loading or impaction (Grade C), functional assessment (mobility, transfers, manual dexterity, dressing and undressing ability, ability to toilet) (Grade A), a screening test for depression (Grade B), and cognitive assessment (to assist in planning and management) (Grade C). The mnemonic DIPPERS (see urinary and fecal incontinence algorithms) covers some of these comorbid conditions. Note that urogenital atrophy does not, in itself, cause urinary incontinence (UI) and should not be treated for this purpose (Grade B). The patient and/or caregiver should be asked about the degree of bother of UI and/or fecal incontinence (Grade B); goals for urinary and fecal incontinence care (dryness, decrease in specific symptoms, quality of life, reduction of comorbidity, lesser care burden) (Grade B); and likely cooperation with management (Grade C).
- Evaluation for bowel “alarm” symptoms (rectal bleeding, positive blood screening from stool studies, obstructive symptoms, recent onset of constipation, weight loss, and a change in stool caliber) will need more extensive evaluation (Grade A).

(*Continued*)

TABLE 14-e5 **Management of Urinary Incontinence in Frail Older Men and Women—Cont'd**

- Urinalysis is recommended for all patients, primarily to screen for hematuria (Grade C). Treatment of otherwise asymptomatic bacteriuria/pyuria is not beneficial (Grade C), and it may cause harm by increasing the risk of antibiotic resistance and severe adverse effects (e.g., *Clostridium difficile colitis*) (Grade C).
- Stool studies may not be needed in all patients with fecal incontinence. Patients with diarrhea, especially those with more acute onset diarrhea, may need to be tested for infectious causes of their diarrhea. Other stool studies could involve testing for malabsorption syndromes.
- The utility of the clinical stress test in this population is uncertain (Grade D).
- Wet checks can assess UI frequency in long-term care residents (Grade C): A post voiding residual volume (PVR) test is impractical in many care settings, and there is no consensus for the definition of what constitutes a high PVR in any population. A PVR measurement is **not** recommended in the routine initial assessment of frail older people with UI.
- However, there is compelling clinical experiential evidence for PVR testing in selected frail older people with diabetes mellitus (especially long standing); prior urinary retention or high PVR; recurrent UTIs; medications that impair bladder emptying (e.g., opiates); severe constipation; persistent or worsening urgency UI despite antimuscarinic treatment; or prior urodynamics showing detrusor underactivity and/or bladder outlet obstruction (BOO) (Grade C). Treatment of contributing comorbidity may reduce PVR. Trial with catheter may be considered for PVR > 200-500 mL if the PVR is felt to contribute to UI or urinary frequency (Grade C).
- **Nocturia** assessment of frail elders with bothersome nocturia should identify potential underlying causes including nocturnal polyuria (by bladder diary/frequency volume chart or wet checks; edema on examination) (Grade C), primary sleep problems (e.g., sleep apnea); and low voided volumes (e.g., from high PVR).
- Stool impaction/loading. If suspected on digital rectal examination (DRE), an abdominal x-ray may be necessary to further evaluate the degree and location of impaction/loading in frail older adults.

TABLE 14-e5 **Management of Urinary Incontinence in Frail Older Men and Women—Cont'd**

**II. Clinical Diagnosis**

The most common types of UI in frail older people are urgency, stress, and mixed UI. Frail older people with urgency UI also may have detrusor underactivity and high PVR (without outlet obstruction). There is no evidence that antimuscarinics are less effective or cause retention in this situation (Grade D).

The most common types of fecal incontinence in frail older people are related to urgency and passive leakage. Passive leakage can refer to leakage, seepage, and staining following bowel movements that are not associated with fecal urgency and may also occur with fecal impaction. Because constipation and impaction often contribute to fecal incontinence in older adults, these are considered separately in the algorithm.

**III. Initial Management**

- Initial treatment should be individualized and influenced by goals of care, treatment preferences, estimated remaining life expectancy, and the most likely clinical diagnosis (Grade C). In some frail older persons the only possible outcome may be containment; management with continence products, especially for people with minimal mobility (require assistance of > two people to transfer), advanced dementia (unable to state their name), and/or nocturnal urinary and fecal incontinence.
- Conservative and behavioral therapy for UI includes lifestyle changes (Grade C), bladder training for more fit and alert persons (Grade B), and prompted voiding for frailer, more impaired older people (Grade A).
- For the select cognitively intact older person with urinary or fecal incontinence, pelvic-floor muscle therapy can be considered, but there are few studies (Grade C). Antimuscarinics may be added to conservative therapy of urgency UI (Grade A-C, depending on agent).
- For the select cognitively intact older with fecal incontinence, biofeedback may be considered, but few studies exist among frail older adults.
- Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction (Grade C). All drugs should be started at the lowest dose and titrated with regular review until either care goals are met or adverse effects are intolerable.

*(Continued)*

TABLE 14-e5 **Management of Urinary Incontinence in Frail Older Men and Women—Cont'd**

- DDAVP (vasopressin) has a high risk of severe hyponatremia in frail older persons and should not be used outside specialist centers (Grade A).
- Improving stool consistency can be done with dietary fiber and supplementary fiber in older adults (Grade C). In older adults with diarrhea, loperamide may be considered at low doses to improve stool consistency. However, close monitoring for constipation and impaction is needed.

**IV. Ongoing Management and Reassessment**

Optimal urinary and fecal incontinence management is usually possible with the above approaches. If initial management fails to achieve the desired goals, the next steps are reassessment and treatment of contributing comorbidity and/or functional impairment.

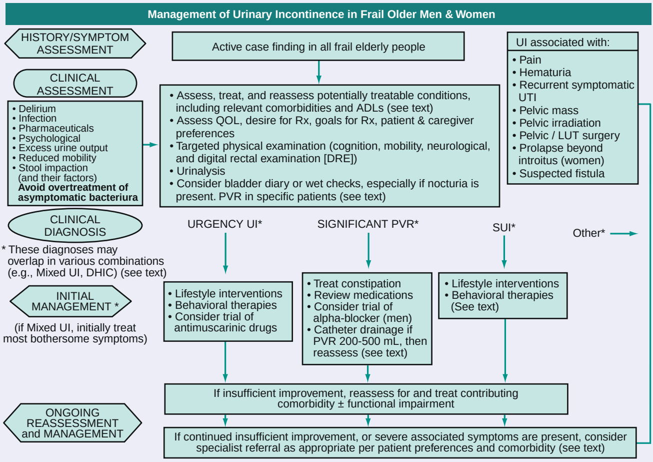
**V. Specialized Management**

If frail older people have either other significant factors (e.g., pain, hematuria, bowel “alarm” symptoms), UI or FI symptoms that cannot be classified as urgency, stress, mixed, or overflow, or other complicated comorbidity that the primary clinician cannot address (e.g., dementia, functional impairment), then specialist referral should be considered. Referral may also be appropriate when there has been insufficient response to initial management. The type of specialist will depend on local resources and the reason for referral: surgical specialists (urologists, gynecologists, colorectal surgeons), gastroenterologists, geriatricians or physical therapists (functional and cognitive impairment); or continence nurse specialists (homebound patients). Referral decisions should consider goals of care, patient/caregiver desire for invasive therapy, and estimated remaining life expectancy.

Age *per se* is not a contraindication to UI or FI surgery (Grade C), but before surgery is considered, all patients should have:

## TABLE 14-e5 Management of Urinary Incontinence in Frail Older Men and Women—Cont'd

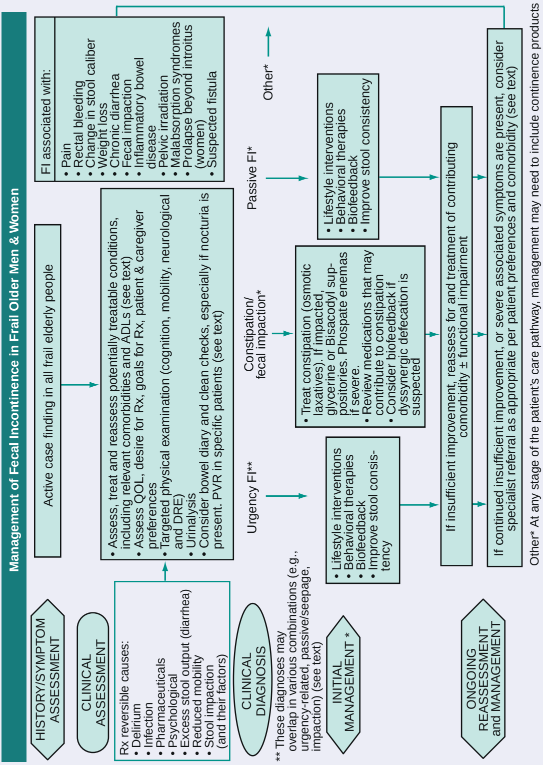
- Evaluation and treatment for any comorbidity, medications, and cognitive or functional impairments contributing to UI that could compromise surgical outcome (e.g., dementia that precludes patient ability to use artificial sphincter) (Grade C)
- Adequate trial of conservative therapy, including pharmacological therapies where relevant (Grade C)
- Discussion (including the caregiver) to ensure that the anticipated surgical outcome is consistent with goals of care in the context of the patient's remaining life expectancy (Grade C)
- Urodynamic testing or anorectal manometry because clinical diagnosis may be inaccurate (Grade B)
- Preoperative assessment and perioperative care to establish risk for and to minimize common geriatric postoperative complications such as delirium and infection (Grade A), dehydration and falls (Grade C).


Management of Urinary Incontinence in Frail Older Men & Women
HISTORY/SYMPTOM ASSESSMENT
Active case finding in all frail elderly people
UI associated with:
• Pain
• Hematuria
• Recurrent symptomatic UTI
• Pelvic mass
• Pelvic irradiation
• Pelvic / LUT surgery
• Prolapse beyond introitus (women)
• Suspected fistula
CLINICAL ASSESSMENT
• Delirium
• Infection
• Pharmaceuticals
• Psychological
• Excess urine output
• Reduced mobility
• Stool impaction (and their factors)
Avoid overtreatment of asymptomatic bacteriura
• Assess, treat, and reassess potentially treatable conditions, including relevant comorbidities and ADLs (see text)
• Assess QOL, desire for Rx, goals for Rx, patient & caregiver preferences
• Targeted physical examination (cognition, mobility, neurological, and digital rectal examination [DRE])
• Urinalysis
• Consider bladder diary or wet checks, especially if nocturia is present. PVR in specific patients (see text)
CLINICAL DIAGNOSIS
* These diagnoses may overlap in various combinations (e.g., Mixed UI, DHIC) (see text)
URGENCY UI*
SIGNIFICANT PVR*
SUI*
Other*
INITIAL MANAGEMENT *
(if Mixed UI, initially treat most bothersome symptoms)
• Lifestyle interventions
• Behavioral therapies
• Consider trial of antimuscarinic drugs
• Treat constipation
• Review medications
• Consider trial of alpha-blocker (men)
• Catheter drainage if PVR 200-500 mL, then reassess (see text)
• Lifestyle interventions
• Behavioral therapies (See text)
ONGOING REASSESSMENT and MANAGEMENT
If insufficient improvement, reassess for and treat contributing comorbidity ± functional impairment
If continued insufficient improvement, or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity (see text)

* At any stage of the patient's care pathway, management may need to include continence products

*(Continued)*

TABLE 14-e5 **Management of Urinary Incontinence in Frail Older Men and Women—Cont'd**


Management of Fecal Incontinence in Frail Older Men & Women
HISTORY/SYMPTOM ASSESSMENT
Active case finding in all frail elderly people
FI associated with:
• Pain
• Rectal bleeding
• Change in stool caliber
• Weight loss
• Chronic diarrhea
• Fecal impaction
• Inflammatory bowel disease
• Pelvic irradiation
• Malabsorption syndromes
• Prolapse beyond introitus (women)
• Suspected fistula
CLINICAL ASSESSMENT
Rx reversible causes:
• Delirium
• Infection
• Pharmaceuticals
• Psychological
• Excess stool output (diarrhea)
• Reduced mobility
• Stool impaction (and their factors)
• Assess, treat and reassess potentially treatable conditions, including relevant comorbidities and ADLs (see text)
• Assess QOL, desire for Rx, goals for Rx, patient & caregiver preferences
• Targeted physical examination (cognition, mobility, neurological and DRE)
• Urinalysis
• Consider bowel diary and clean checks, especially if nocturia is present. PVR in specific patients (see text)
CLINICAL DIAGNOSIS
** These diagnoses may overlap in various combinations (e.g., urgency-related, passive/seepage, impaction) (see text)
Urgency FI**
Constipation/ fecal impaction*
Passive FI*
Other*
INITIAL MANAGEMENT *
• Lifestyle interventions
• Behavioral therapies
• Biofeedback
• Improve stool consistency
• Treat constipation (osmotic laxatives). If impacted, glycerine or Bisacodyl suppositories. Phospate enemas if severe.
• Review medications that may contribute to constipation
• Consider biofeedback if dyssynergic defecation is suspected
• Lifestyle interventions
• Behavioral therapies
• Biofeedback
• Improve stool consistency
ONGOING REASSESSMENT and MANAGEMENT
If insufficient improvement, reassess for and treatment of contributing comorbidity ± functional impairment
If continued insufficient improvement, or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity (see text)
Other* At any stage of the patient's care pathway, management may need to include continence products

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e6 **Management of Neurogenic Incontinence**
A. Initial Management

**I. Strong General Recommendations**

- Patients with known neurological disease often need evaluation to exclude bladder dysfunction, not only if symptoms occur, but as a standard assessment because *neurogenic bladder* has a high prevalence in this disease (for prevalence figures, see chapter).
- *A possible neurological* cause of "idiopathic" incontinence should always be considered. Diagnostic steps to evaluate this include basic assessments, such as history and physical examination, urodynamics, and specialized tests.
- *Incontinence in neurological* patients does *not necessarily relate* to the neurologic pathology. *Other diseases,* such as prostate pathology and pelvic organ prolapse, might have an influence. These have to be ruled out.
- *Extensive diagnostic evaluation* is often useful and necessary to tailor an individual treatment based on complete neurofunctional data. This *may not be needed in every patient* (e.g., patients with suprapontine lesions or patients in whom treatment will consist merely of bladder drainage due to a bad medical condition or limited life expectancy).
- There is often a need to manage *bladder* and *bowel* together.

**II. Initial Assessment**

- The management of neurological urinary incontinence (UI) depends on an *understanding of the likely mechanisms producing incontinence.* This can, in turn, depend on the *site and extent of the nervous system abnormality.*
- Therefore neurogenic incontinence patients can be divided into those having:
    - *Peripheral lesions* (as after major pelvic surgery), including those with lesions of the cauda equina (e.g., lumbar disk prolapse)
    - *Sacral spinal cord lesions involving the sacral micturition center*
    - *Suprasacral spinal cord lesions* (suprasacral infrapontine spinal cord lesions)
    - *Central lesions of the brain or brainstem* (stroke, Parkinson disease)
- *History* and *physical examination* are important in helping *distinguish* these groups.

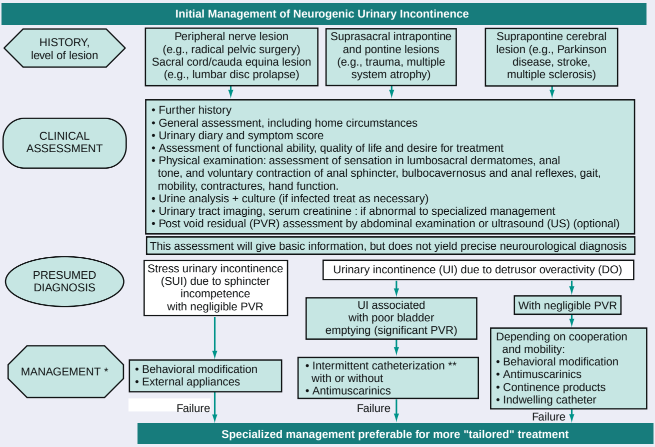
(*Continued*)

TABLE 14-e6 **Management of Neurogenic Incontinence**
A. Initial Management—Cont'd

**III. Initial Treatment**

Patients with *peripheral nerve lesions* (e.g., denervation after pelvic surgery) and patients with *spinal cord lesions* (e.g., traumatic spinal cord lesions) should get *specialized management* (A).

Initial treatment for patients with incontinence due to *suprapontine pathology* such as stroke need to be assessed for degree of mobility and ability to cooperate. Initial recommended treatments are behavioral therapy (C) and antimuscarinic drugs for presumed detrusor overactivity (DO) (A). Continence products (B) or catheters (C) may be necessary for uncooperative or less mobile patients.


Initial Management of Neurogenic Urinary Incontinence
HISTORY, level of lesion
Peripheral nerve lesion (e.g., radical pelvic surgery) Sacral cord/cauda equina lesion (e.g., lumbar disc prolapse)
Suprasacral intrapontine and pontine lesions (e.g., trauma, multiple system atrophy)
Suprapontine cerebral lesion (e.g., Parkinson disease, stroke, multiple sclerosis)
CLINICAL ASSESSMENT
• Further history
• General assessment, including home circumstances
• Urinary diary and symptom score
• Assessment of functional ability, quality of life and desire for treatment
• Physical examination: assessment of sensation in lumbosacral dermatomes, anal tone, and voluntary contraction of anal sphincter, bulbocavernosus and anal reflexes, gait, mobility, contractures, hand function.
• Urine analysis + culture (if infected treat as necessary)
• Urinary tract imaging, serum creatinine : if abnormal to specialized management
• Post void residual (PVR) assessment by abdominal examination or ultrasound (US) (optional)
This assessment will give basic information, but does not yield precise neurourological diagnosis
PRESUMED DIAGNOSIS
Stress urinary incontinence (SUI) due to sphincter incompetence with negligible PVR
Urinary incontinence (UI) due to detrusor overactivity (DO)
UI associated with poor bladder emptying (significant PVR)
With negligible PVR
MANAGEMENT *
• Behavioral modification
• External appliances
• Intermittent catheterization ** with or without
• Antimuscarinics
Depending on cooperation and mobility:
• Behavioral modification
• Antimuscarinics
• Continence products
• Indwelling catheter
Failure
Failure
Failure
Specialized management preferable for more "tailored" treatment

* At any stage of the patient's care pathway, management may need to include continence products
** Some patients omit IC through personal choice or inability to self-catheterize

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e7 **Management of Neurogenic Incontinence**
B. Specialized Management

**I. Assessment**

- Most patients with neurogenic urinary incontinence (UI) require specialized assessment: ***Urodynamic studies should be used*** with video urodynamics if available when surgical interventions are planned or when the "bladder may be unsafe."
- ***Upper tract imaging*** is needed in some patients, and more detailed renal function studies will be desirable if the upper tract is considered in danger: high bladder pressure, upper urinary tract dilatation, recurrent or chronic upper tract infection, (major) stones, (major) reflux.
- In patients with ***peripheral lesions,*** clinical ***neurophysiological testing*** may be helpful for better definition of the lesion.

**II. Treatment**

***Also for specialized management, conservative treatment is the mainstay***

*(A)*. Management of neurogenic UI has several therapeutic options. The algorithm details the recommended options for different types of neurological dysfunction of the lower urinary tract (LUT). The dysfunction does not necessarily correspond to one type or level of neurological lesion but ***must depend*** mostly on ***urodynamic findings***. One should always ascertain that the management is *urodynamically safe* (low pressure, complete emptying).

It is recommended to look at ***urinary*** and ***bowel*** function ***together*** if both systems are affected because symptoms and treatment of one system can influence the other and vice versa (A).

Because therapeutic approaches can differ in various neurological diseases, the most prevalent diseases are discussed separately in the chapter.

**III. Treatment Modalities (often in combination)**

*Conservative*

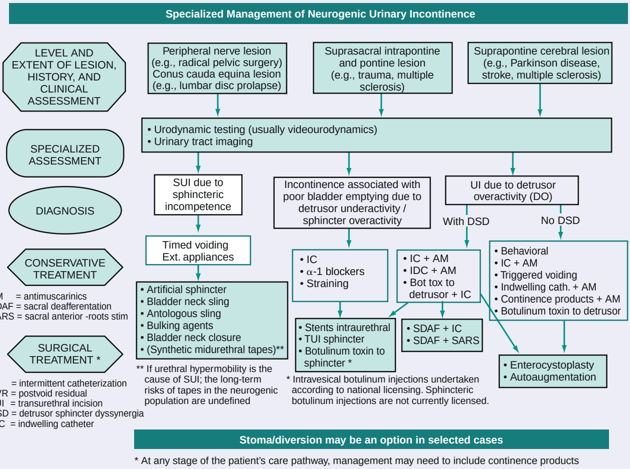
- Intermittent catheterization (A)
- Behavioral treatment (C)
- Timed voiding (C)
- Continence products (B)
- Antimuscarinics (A)
- Alpha-1 adrenergic blockers (C)
- Intravesical electrical stimulation (C)
- Bladder expression (B)
- Triggered voiding (C)
- Indwelling catheter (C)
- Artificial sphincter (A)

(*Continued*)

TABLE 14-e7 **Management of Neurogenic Incontinence**
B. Specialized Management—Cont'd

*Surgical treatment*

- Bladder neck Sling (B)
- Suburethral tapes (D)
- Bulking agents (D)
- Bladder neck closure (D)
- Stents intraurethral (B)
- TUI sphincter (B)
- Botulinum toxin for: sphincter (C), detrusor (A)
- Sacral deafferentation (B)
- Sacral anterior root stimulator (B)
- Enterocystoplasty (B)
- Autoaugmentation (D)


Specialized Management of Neurogenic Urinary Incontinence
LEVEL AND EXTENT OF LESION, HISTORY, AND CLINICAL ASSESSMENT
Peripheral nerve lesion (e.g., radical pelvic surgery) Conus cauda equina lesion (e.g., lumbar disc prolapse)
Suprasacral intrapontine and pontine lesion (e.g., trauma, multiple sclerosis)
Suprapontine cerebral lesion (e.g., Parkinson disease, stroke, multiple sclerosis)
SPECIALIZED ASSESSMENT
• Urodynamic testing (usually videourodynamics)
• Urinary tract imaging
DIAGNOSIS
SUI due to sphincteric incompetence
Incontinence associated with poor bladder emptying due to detrusor underactivity / sphincter overactivity
UI due to detrusor overactivity (DO)
With DSD
No DSD
CONSERVATIVE TREATMENT
Timed voiding
Ext. appliances
• IC
• α-1 blockers
• Straining
• IC + AM
• IDC + AM
• Bot tox to detrusor + IC
• Behavioral
• IC + AM
• Triggered voiding
• Indwelling cath. + AM
• Continence products + AM
• Botulinum toxin to detrusor
AM = antimuscarinics
SDAF = sacral deafferentation
SARS = sacral anterior -roots stim
SURGICAL TREATMENT *
• Artificial sphincter
• Bladder neck sling
• Antologous sling
• Bulking agents
• Bladder neck closure
• (Synthetic midurethral tapes)**
• Stents intraurethral
• TUI sphincter
• Botulinum toxin to sphincter *
• SDAF + IC
• SDAF + SARS
• Enterocystoplasty
• Autoaugmentation
** If urethral hypermobility is the cause of SUI; the long-term risks of tapes in the neurogenic population are undefined
* Intravesical botulinum injections undertaken according to national licensing. Sphincteric botulinum injections are not currently licensed.
IC = intermittent catheterization
PVR = postvoid residual
TUI = transurethral incision
DSD = detrusor sphincter dyssynergia
IDC = indwelling catheter
Stoma/diversion may be an option in selected cases
* At any stage of the patient's care pathway, management may need to include continence products

(*From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

TABLE 14-e8 **International Consultation on Incontinence Assessments 2013: Oxford Guidelines (Modified)**

***Levels of Evidence***

**Level 1:** Evidence (incorporates Oxford 1a and 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomized controlled trial, or "all or none" studies in which no treatment is not an option (e.g., in vesicovaginal fistula).

**Level 2:** Evidence (incorporates Oxford 2a, 2b, and 2c) includes "low" quality RCT (e.g., < 80% follow-up) or meta-analysis (with homogeneity) of good quality prospective cohort studies. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

**Level 3:** Evidence (incorporates Oxford 3a, 3b, and 4) includes:

Good quality retrospective "case-control studies" in which a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition.

Good quality "case series" in which a complete group of patients with the same condition/disease/therapeutic intervention are described without a comparison control group.

**Level 4:** Evidence (incorporates Oxford 4) includes expert opinion when the opinion is based not on evidence but on "first principles" (e.g., physiological, anatomical) or bench research. The Delphi process can be used to give "expert opinion" greater authority. In the Delphi process, a series of questions are posed to a panel; the answers are collected into a series of "options"; the options are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made.

***Grades of Recommendation***

**Grade A:** Recommendation usually depends on consistent Level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions when excellent evidence (level 1) does not lead to a Grade A recommendation (e.g., if the therapy is prohibitively expensive, dangerous, or unethical). Grade A recommendation can follow from Level 2 evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level 1 evidence.

**Grade B:** Recommendation usually depends on consistent Level 2 and/or 3 studies or "majority evidence" from RCTs.

(*Continued*)

TABLE 14-e8 **International Consultation on Incontinence Assessments 2013: Oxford Guidelines (Modified)—Cont'd**

**Grade C:** Recommendation usually depends on Level 4 studies or "majority evidence" from Level 2 or 3 studies or Dephi processed expert opinion.

**Grade D:** "No recommendation possible" would be used when the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Dephi.

*(From Abrams P, Cardozo L, Khoury S, et al, editors:* Incontinence, *ed 5, Arnhem, The Netherlands, 2013, European Association of Urology and International Consultation on Urological Diseases.)*

## CHAPTER 15

# Benign Prostatic Hyperplasia and Related Entities

Stephen Mock, MD • Roger Dmochowski,
MD, MMHC, FACS

## General Considerations

The evaluation and management of symptoms related to bladder outlet and urethral obstruction are responsible for a large portion of any given urology practice. An etiologic categorization is seen in Table 15-1. Although some of these entities may be associated with abnormalities of the urinary sediment or a characteristic finding on physical examination, most present only with lower urinary tract symptoms (LUTS). The symptoms are remarkably nonspecific and are associated more so with some entities rather than others strictly because of their prevalence.

This chapter considers the most common of these, benign prostatic hyperplasia (BPH), and its related entities: benign prostatic enlargement (BPE) and benign prostatic obstruction (BPO). Bladder neck and smooth sphincter dyssynergia or dysfunction and striated sphincter dyssynergia have been previously considered in Chapter 14, and urethral stricture disease in Chapter 11.

## Definitions and Epidemiology

**BPH refers to a regional nodular growth of varying combinations of glandular and stromal proliferation that occurs in almost all men who have testes and who live long enough.** Because of the anatomic localization of the prostatic growth that characterizes BPH — surrounding and adjacent to the proximal urethra — clinical problems can result. BPH can be defined in a number

TABLE 15-1 **Bladder Outlet and Urethral Obstruction: Etiology**

***Prostate***

- Benign prostatic enlargement
- Cancer
- Other infiltrative processes

***Bladder Neck and Proximal Urethra***

- Contracture, fibrosis, stricture, stenosis
- Dyssynergia/dysfunction
  - Smooth sphincter
  - Striated sphincter
- Secondary hypertrophy of bladder neck
- Compression
- Distended vagina and uterus
- Extrinsic tumor
- Calculus, mucus, foreign body
- Ectopic ureterocele
- Polyp
- Posterior urethral valve

***Distal Urethra***

- Contracture, fibrosis, stricture, stenosis, calculus, foreign body
- Anterior urethral valve

of ways, depending on the orientation of the user of the term. **Microscopic BPH** refers to the histologic evidence of cellular proliferation. **Macroscopic BPH** refers to organ enlargement due to the cellular changes. BPH histopathologically is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate, the molecular etiology of which is uncertain. The incidence of histologic or microscopic BPH is far greater than that of clinical or macroscopic BPH. BPH has also been referred to as *hyperplasia*, *benign prostatic hypertrophy, adenomatous hypertrophy, glandular hyperplasia,* and *stromal hyperplasia*.

Historically, the term *prostatism* was applied to almost all symptoms that reflected a micturition disorder in the older man. The term unfortunately implied that the cause of the problem was the prostate, which, in later years was found clearly not to be the case in many instances. The World Health Organization (WHO) sponsored consultations on BPH and has recommended changes to the terminology related to urinary symptoms and the prostate in elderly men. The term *LUTS (lower urinary tract symptoms)* was introduced by Paul Abrams and has been adopted as the proper terminology to apply to any patient, regardless of age or sex, with urinary symptoms but without implying the underlying problem. **LUTS were initially divided into "irritative" and "obstructive" symptoms, but it became obvious that there was a poor correlation between so-called obstructive symptoms and a urodynamic diagnosis of bladder outlet obstruction (BOO) and also between so-called irritative symptoms and a urodynamic diagnosis that related to definable abnormalities seen during filling and storage.** Additionally, the term *irritative* implied to some people an infectious or inflammatory process. Thus **the division of LUTS into "filling/storage symptoms and emptying/voiding symptoms" evolved.** (See Chapter 14.)

The terminology with respect to prostate characteristics has also changed. Paul Abrams was the first to suggest a reconsideration of the use of the term *BPH* and a redefinition of the terminology. He pointed out that BPH was a histologic diagnosis that had been shown to occur in 88% of men older than 80 years. He added that, in some patients, the prostate gland enlarged, and this condition should be distinguished from BPH and referred to as *BPE*. In approximately half of these patients with BPE, he stated that true BOO resulted, a condition that should be termed *BPO*. BPH was previously an all-encompassing term that included prostate size, benign prostate histology, and all filling/storage or voiding/emptying symptoms thought to be related to the prostate pathophysiologically in the adult male. The current terminology recognizes the imprecise and misleading implications of the initial usage of this phrase. The terminology related to the prostate is currently expressed as follows:

1. **BPH** — benign prostatic hyperplasia: This term is used and reserved for the typical histopathologic pattern that defines the condition.
2. **BPE** — benign prostatic enlargement: This refers to the size of the prostate, specifically the prostatic enlargement due to a benign cause, generally histologic BPH. If there is no prostatic histologic examination available, the term *prostatic enlargement* should be used.
3. **BPO** — benign prostatic obstruction: This is a form of BOO. This term may be applied when the cause of the

outlet obstruction is known to be BPE due to a benign cause, generally histologic BPH. *BOO* is a functional term for any cause of subvesical obstruction. The WHO-sponsored consultation on BPH recommended the generic phrase *LUTS suggestive of BPO* to describe elderly men with filling/storage or voiding/emptying problems likely to be caused by an obstructing prostate. It should be noted that there are other causes of BOO than prostatic enlargement (see Table 15-1).

Autopsy data indicate that anatomic (microscopic) evidence of BPH is seen in about 25% of men 40 to 50 years of age, 50% of men ages 50 to 60, 65% of men ages 60 to 70, 80% of men ages 70 to 80, and 90% of men ages 80 to 90.

Estimates of the prevalence of clinical BPH vary widely, probably because of the varying thresholds used to define the presence of BPH on the basis of symptoms and/or urodynamics (no uniform definition) or on the basis of the rate of prostatic surgery. It has been classically stated that 25% to 50% of individuals with microscopic and macroscopic evidence of BPH will progress to clinical BPH. Depending on which definition is used, the prevalence of clinical BPH in an individual community in men ages 55 to 74 years may vary from less than 5% to more than 30%. Only 40% of this group, however, complain of LUTS, and only about 20% seek medical advice because of them. The number of individuals who receive treatment for clinical BPH varies according to the threshold for providing such treatment, a threshold that can vary widely in different parts of the world and in different parts of the United States. As treatments become less invasive, this number can be expected to rise.

**Only age and the presence of testes are positively correlated with the development of BPH.** Obesity may be positively correlated with prostate volume. Most agree that cirrhosis is inversely correlated, probably because of decreased plasma testosterone (T) levels. **A positive association between LUTS secondary to BPO and erectile dysfunction (ED) seems to be real, but whether this is simply age related or not is less certain.** There are no consistent correlations for dietary factors, vasectomy, prior sexual history, smoking, or other disease states. **BPH does appear to have an inheritable genetic component,** although the specifics are yet to be elucidated.

## Prostatic Size and Morphology Pertinent to BPH

Although some prostatic growth occurs throughout life, the prostate changes relatively little in size until puberty, when it undergoes rapid growth. Autopsy studies indicate that the normal adult prostate plateaus at a volume of approximately 25 mL at age 30. This remains relatively stable until approximately age 50, after which increasing volume is observed, such that the average prostate volume is approximately 35 to 45 mL at age 80.

Throughout developmental life the prostate maintains its ability to respond to endocrine signals, undergoes rapid growth at puberty, and maintains its size and tissue androgen-receptor levels. In some individuals, abnormal growth subsequently occurs, which may be either benign or malignant. The mechanisms of normal and abnormal growth have yet to be resolved but are thought to involve multiple growth promoting and inhibiting factors ultimately controlling cell replication, cell cycle control, cell aging, cell senescence, and cell death, both necrosis and apoptosis. A full discussion of the factors relating to prostate physiology and growth can be found in *Campbell-Walsh Urology,* 10th edition, Chapter 90, “Development, Molecular Biology, and Physiology of the Prostate.”

**The size of the prostate is not linearly correlated to either urodynamic evidence of BOO or the severity of symptoms.**

The adult prostate is a truncated cone with its base at the urethrovesical junction and its apex at the urogenital diaphragm. The prostate is pierced by the urethra, which angles forward at the verumontanum, and by the paired ejaculatory ducts, which join the urethra at its point of angulation. A lobular configuration of the prostate was originally described by Lowsley, based on studies of the human fetal prostate. A posterior, two lateral, an anterior, and a middle lobe were described. Although this description was used by urologists for years because it seemed to bear some relationship to endoscopic and gross surgical anatomy, **distinct lobes do not exist in the prepubertal and normal adult prostate.** The concept of a lobular structure has been replaced by one based on concentric zones that have morphologic, functional, and pathologic significance. McNeal and associates from Stanford have done the most to expand our understanding of adult prostate morphology, describing the zonal anatomy based on examination of the gland in different planes of section (Figure 15-1). The urethra represents the primary reference point, dividing the prostate into an anterior fibromuscular and a posterior glandular portion. The anterior fibromuscular stroma comprises up to one third of the total bulk of the prostate. It contains no glandular element. This fibromuscular stroma has not been linked to a specific pathologic process. The two principal regions of the glandular prostate are defined as the peripheral zone (approximately 75% of total glandular volume) and the central zone (approximately 25%), each morphometrically distinct. The central zone makes up about 25% of the functioning glandular prostate. It contains the urethra only at the upper end of the veru, where its ducts open. The development of carcinoma is relatively uncommon in this area. **The peripheral zone is the site of origin of most prostate cancer. The glandular tissue that participates in the BPH nodule formation is derived exclusively from the branches of a few small ducts, representing approximately 5% to 10% of the glandular prostate, that join the urethra at or proximal to its point of angulation.** Urethral angulation at the most proximal extent of the verumontanum displaces the proximal urethral segment from the secretory gland mass anteriorly and into the anterior fibromuscular stroma. The resulting space between the urethra and glandular prostate accommodates a cylindrical smooth muscle sphincter that surrounds the proximal segment of the urethra from the base of the verumontanum to the bladder neck. All nodules of BPH develop within or immediately adjacent to this smooth muscle layer, and this tissue is subdivided by this muscle into two discrete regions. The transitional zone comprises less than 5% to 10% of the total glandular volume and consists of two separate lobules of tissue immediately outside of the smooth muscle layer, located laterally and extending somewhat ventrally. A tiny periurethral region (less than 1% of the total glandular prostate) contains glands that are entirely contained within the smooth muscle layer from just proximal to the point of urethral angulation to the bladder neck. This periurethral zone is so small that it is not pictured in many other renditions of McNeal's zonal anatomy. The origin of BPH is confined exclusively to these areas, and some cancers may also originate here. Between the transitional and peripheral zones are the central zones, which have not been implicated in the origin of a specific pathologic process.

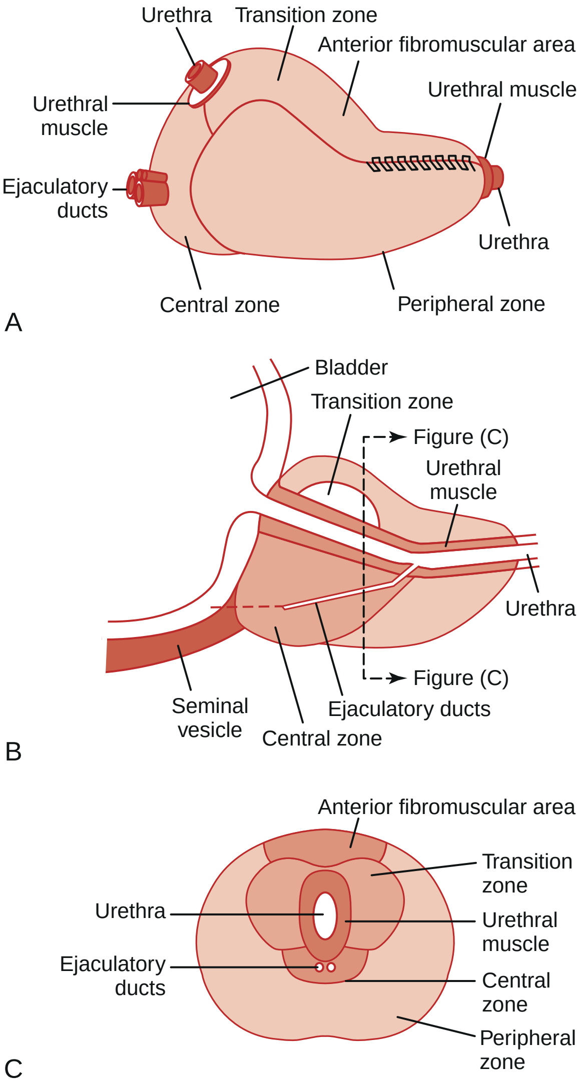


**FIGURE 15-1 Prostatic zonal anatomy after McNeal. Schematic (A), sagittal cross-section (B), transverse cross-section (C).** (From Hanno P, Malkowicz SB, Wein A, editors: *Benign prostatic hyperplasia, clinical manual of urology,* New York, 2001, McGraw Hill, F15–1, p 441.)

## Etiologic Theories of BPH: Pathophysiology

Clinically detectable BPH nodules arise from a variety of adenomas in the transitional and periurethral zones. As these grow, they may outwardly compress the anterior fibromuscular stroma and areas in the peripheral and central zones. A so-called **surgical capsule** develops between the hyperplastic nodules and the compressed glandular tissue and serves as a plane of cleavage. This serves as a useful landmark in open or transurethral surgical treatment. The etiologic factors responsible for BPH nodule induction and further development are unclear. However, a number of factors are obviously involved, although the magnitude of their importance and their interactions remains to be fully elucidated. What follows is the briefest of descriptions of the major factors mentioned, gleaned mostly from the work of Walsh, Coffey, and their group at Johns Hopkins; Grayhack, Lee, and the group at Northwestern; and Cunha and others. A complete discussion of prostate physiology and the pathophysiology of BPH can be found in Chapters 90 and 91 of *Campbell-Walsh Urology,* 10th edition ("Development, Molecular Biology, and Physiology of the Prostate" and "Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History").

### HORMONES

There is no question that a functioning testis is a prerequisite for the normal development of the prostate in animals and humans. Males castrated before puberty do not develop BPH. BPH is rare in males castrated before the age of 40. Androgen deprivation in older men reduces prostate size. Patients with diseases that result in impaired androgenic production or metabolism have reduced or minimal prostatic growth. Although other endocrine factors are no doubt involved, the androgenic influence on prostatic growth and function is obviously central, although endocrine evaluation of the aging male has disclosed no recognizable surge in androgen secretion. The prostate develops from the urogenital sinus during the third fetal month under the influence of dihydrotestosterone (DHT) produced from fetal T via 5-alpha reductase. During development there is a close but incompletely understood interaction between the stromal and epithelial components. DHT is produced from T in the stroma cell and has an autocrine effect there and a paracrine effect in the epithelial cell. These effects are thought to include induction of multiple growth factors and alteration in the extracellular matrix. Prostate growth and maintenance of size and secretory function are stimulated by serum T, converted within the prostate to DHT, a compound whose relative androgenicity is higher. Free plasma T enters prostatic cells by diffusion and is rapidly metabolized to other steroids. More than 90% is irreversibly converted to the main prostatic androgen, DHT, by the enzyme 5-alpha reductase. DHT or T is bound to specific androgen receptors in the nucleus, when activation of the steroid receptor occurs.

Originally, an abnormal accumulation of DHT in the prostate was hypothesized as a primary cause of BPH development. However, Coffey and Walsh showed that human BPH occurs in the presence of normal prostatic levels of DHT. Estrogen-androgen synergism has been postulated as necessary for prostatic growth, as have other steroid hormones and growth factors. Although much remains to be elucidated regarding the hormonal interactions and necessities for the induction and maintenance of BPH, it is clear that clinically a reduction in prostate size of approximately 20% to 30% can be induced by either interfering with androgen-receptor binding or metabolism.

## STROMAL-EPITHELIAL INTERACTION THEORY

This theory, first introduced by Cunha and associates, postulates that a delicate stromal-epithelial balance exists in the prostate and that stroma may mediate the effects of androgen on the epithelial component, perhaps by the production of various growth factors and/or autocrine and paracrine messengers.

## STEM-CELL THEORY

This is attributed to Issacs and associates and hypothesizes that BPH may result from abnormal maturation and regulation of the cell renewal process. In simple terms, this postulates that abnormal size in an aged prostate is maintained not by the increase in the rate of cell replication but rather by a decrease in the rate of cell death. Hormonal factors, growth factors, and oncogenes all influence this balance of replication and cell death. The exact interaction of these and possibly other factors and what determines the setting points for the level of cells in the prostate and their rates of growth, replication, and death are of major importance in understanding both BPH and prostate cancer.

## STATIC AND DYNAMIC COMPONENTS OF PROSTATIC OBSTRUCTION

It is extremely important to understand the concepts of the two prostatic components contributing to BOO caused by BPO. The **static component** is due to bulk and includes elements of the stromal and epithelial cells and extracellular matrix. Androgen ablation, at least in short-term studies, affects primarily the epithelial cell population volume. Long-term effects on stromal and matrix volume and effects on aspects of stroma and matrix other than volume have not been excluded, however. Therapeutic modalities that reduce the size of the prostate or “make a hole” or enlarge one are directed primarily toward this bulk component.

The **dynamic component** of obstruction refers to the contribution of prostatic smooth muscle. The tension of prostatic smooth muscle is mediated by alpha-1 adrenergic receptors, most of which are in the prostatic stroma. Alpha-1 receptors also exist in the smooth muscle of the bladder neck and the prostatic capsule. Activation of these contractile receptors can occur either through circulating catecholamine levels or through adrenergic innervation. Prostatic intraurethral pressure can be reduced experimentally by as much as 40% after systemic administration of an alpha-receptor antagonist. This dynamic component may be responsible for the well-recognized variation in symptoms over time experienced by many patients and may account for exacerbation of symptoms experienced by some individuals in response to certain foods, beverages, change in temperature, and levels of stress.

This two-component idea was first popularized by Marco Caine and later developed by Herb Lepor and Ellen Shapiro, resulting in the successful application of selective alpha-adrenergic blocking agents for the treatment of BPH symptoms. **The ratio of stroma to epithelium in the normal prostate is approximately 2:1, and in BPH approximately 5:1.** These data for BPH are derived primarily from small resected prostates; the ratio for larger glands with epithelial nodules may be lower. Although the smooth muscle content of stroma has not been precisely determined, a significant proportion of the stroma is in fact smooth muscle.

## Lower Urinary Tract Symptoms

*LUTS* is a rubric, introduced by Abrams, to replace the term *prostatism*, which implied that the prostate was responsible for most (or all) symptomatic voiding complaints in men. LUTS with its subdivisions, filling/storage symptoms and voiding/emptying symptoms, have replaced the terminology of *irritative* and *obstructive* symptoms, both rather imprecise terms that imply an etiology that may be incorrect. **Voiding/emptying symptoms include impairment in the size and force of the urinary stream, hesitancy and/or straining to void, intermittent or interrupted flow, a sensation of incomplete emptying, and terminal dribbling, although the last by itself seems to have little clinical significance. Filling/storage symptoms include nocturia, daytime frequency, urgency, and urgency incontinence. Emptying/voiding symptoms are the most prevalent, but filling/storage symptoms are the most bothersome to the patient** and interfere to the greatest extent with daily life activities.

LUTS associated with BPE and BPO are, however, not simply solely due to BOO. Such symptoms are due, in varying proportions in different individuals, to obstruction, obstruction-related changes in detrusor structure and function, age-related changes in detrusor structure and function, and changes in neural circuitry that may occur secondary to these factors.

## Signs of BPH

1. Detectable anatomic **enlargement of the prostate** on physical examination or imaging is generally, but not always, the correlate of symptom-producing BPH. However, **no clear relationship exists between the degree of anatomic enlargement and the severity of urodynamic changes.**
2. **Bladder changes** secondary to obstruction can occur. These consist of **bladder wall thickening, trabeculations** (which are also associated with involuntary bladder contractions), and **bladder diverticula** (which could also be congenital). Bladder **calculi** can develop. Bladder **decompensation** can occur, and gross bladder **distention** can result. Chronically increased residual urine volumes may result and may contribute to frequency and urgency and persistent urinary

infection. Acute urinary retention may supervene. Azotemia may result from upper tract changes. There is an increased incidence of lower urinary tract infections (UTIs) in obstructed patients.

3. **Upper tract changes** of ureterectasis, hydroureter, and/or hydronephrosis can result. These can result either from secondary vesicoureteral reflux, sustained high-pressure bladder storage without reflux, and sustained high-pressure attempts at emptying. Ureteral obstruction could also occur secondary to muscular hypertrophy or angulation at the ureterovesical junction. Hematuria may arise from dilated veins coursing over the surface of the enlarged adenomatous prostate.

## Urodynamics of BOO

The urodynamics of BOO are described in Chapter 14. Patients with BPO characteristically exhibit decreased mean and peak flow rates, an abnormal flow pattern characterized by a long, low plateau, and elevated detrusor pressures at the initiation of and during flow. They may or may not have residual urine. Approximately 50% of such patients are found to have detrusor overactivity during filling. Pressure-flow urodynamics testing (UDS) can demonstrate detrusor underactivity. In this circumstance, it usually cannot be determined whether obstruction exists or existed prior, accounting for the detrusor dysfunction — a major issue. Specialized variations of UDS, either with or without video, are often helpful to separate BPO from other forms of outlet obstruction (see Chapter 14).

### RESIDUAL URINE VOLUME

If the residual urine volume is significant, its reduction is important in the evaluation of results of treatment of BPO. For many with a significant residual volume, it is impossible to differentiate deficient bladder contractility from outlet obstruction as the primary cause, without a pressure-flow study. Most agree that a large residual urine volume reflects a degree of bladder dysfunction, but it is difficult to correlate residual urine with either specific symptomatology or other urodynamic abnormalities. The most popular noninvasive method of measurement is ultrasonography. The error for ultrasound has been estimated at 10% to 25% for bladder volumes greater than 100 mL and somewhat worse for smaller volumes. Residual urine volumes in an individual patient at different times can vary widely. Reflux and large diverticula may complicate the accuracy of measurement. Paul Abrams and colleagues, after a thorough review of the subject, concluded that elevated residual urine has a relation to prostatic obstruction, although not a strong one, as supported by the following observations.

1. Elevated residual urine is common in the elderly of both genders.
2. The absence of residual urine does not rule out severe obstruction.
3. Elevated residual urine does not have a significant prognostic factor for a good operative outcome. Volume of more than 300 mL may correlate with unfavorable outcome.

What constitutes an abnormal residual urine? The International Consultation on BPH concluded that a range of 50 to 100 mL represents the lower threshold to define abnormal. There is discussion ongoing as to the concept that it may be more clinically meaningful to describe residual urine volume as a percent of bladder capacity rather than as an absolute number.

## UROFLOWMETRY

Significant disagreement exists regarding what constitutes an adequate urodynamic evaluation of LUTS in the male and whether a urodynamically quantifiable definition of obstruction is necessary or desirable before beginning treatment. Of all these urodynamic studies, uroflowmetry seems to excite the least controversy. **Although diminished flow may be caused by either outlet obstruction or impairment of detrusor contractility, and outlet obstruction may certainly exist in the presence of a normal flow, it is acknowledged that most men with BOO do have a diminished flow rate and altered flow pattern.**

**What is a normal flow rate?** Paul Abrams and Derek Griffiths originally proposed that, empirically, peak flow rates of less than 10 mL/sec were associated with obstruction, peak flow rates greater than 15 mL/sec were not associated with obstructed voiding, and peak flow rates between 10 and 15 mL/sec were equivocal. Although this proposal has been widely used, it is generally acknowledged that flow rates at any level may be associated with either obstruction or lack of obstruction. Studies are cited showing that 7% to 25% of patients referred with LUTS had high flow BOO.

**Potential problems related to uroflow include the following:**

1. Many patients do not or will not void in a volume sufficient for accurate measurement.
2. Others void with an interrupted stream or with postvoid dribbling, which makes interpretation of the endpoint of micturition difficult, casting some element of subjectivity into the calculation of average flow rate.
3. Some patients are unable to relax sufficiently to void in the same manner in which they would in the privacy of their own bathroom.
4. A considerable discrepancy may exist between the first and subsequent measures of mean and peak flow.
5. The flow parameter measured noninvasively and in the course of pressure flow studies in the same individual may vary considerably.

Flow data changes can be expressed in terms of absolute change, percent change, or as cumulative frequency distribution. Clearly important is the initial flow number, the value of which may make the absolute or percent change look better or worse. In other words, raw data must be expressed along with the other frills that may be added to embellish flow data. It should be noted also that **it is unknown what change in flow is necessary to give the impression of mild, moderate, or marked improvement.**

Because voiding events may be different from point to point in an individual's life, a variety of flow nomograms have been constructed to facilitate comparison of them. It should be noted that many nomograms and tables of "acceptable flow rates" are available for various age groups. Many believe that the Siroky nomogram, commonly used in the United States, overestimates peak and average flow rates for older men and therefore underestimates the number of older men with BOO. Other nomograms include the Drach peak-flow nomogram and the Liverpool and Bristol nomograms. It is doubtful that consistency will be achieved among flow nomogram makers. However, one of the systems supported by at least a portion of urodynamicists should be utilized for comparison following treatment of BPO.

## CYSTOMETRY AND PRESSURE-FLOW STUDIES

Filling cystometry provides information on sensation, compliance, and the presence of and threshold for involuntary bladder contractions and urodynamic bladder capacity. Compliance is generally not affected in patients with BPO, but as mentioned previously, approximately 50% of such patients will have involuntary bladder contractions.

On a logical basis, BOO would seem to be defined by the relationship between flow rate and detrusor contractility. **Outlet obstruction is best characterized by a poor flow rate in the presence of a detrusor contraction of adequate force, duration, and speed. With obstruction, detrusor pressure during attempted voiding generally rises, flow rates generally fall, and the shape of the flow curve becomes more like a plateau than a parabola.** However, marked disagreement exists about the utility of pressure-flow urodynamic measurements in the prediction of success of a given treatment and in the assessment of treatment results. Authorities who make an excellent case for the use of various types of pressure-flow studies in evaluating patients with LUTS and favorably affecting outcomes include Abrams and associates; Blaivas, Coolsaet, and Blok; Jensen, Neal, and colleagues; Schafer and coworkers; and Rollema and Van Mastrigt. Some add other mathematical means to augment the relationships observed on a simple plot of detrusor pressure versus flow. Equally forceful arguments against the utility of such measurements are made by Andersen, Bruskewitz, and colleagues; Graverson and coworkers; and McConnell. Jensen did an exhaustive review of the subject of urodynamic efficacy in the evaluation of elderly men with prostatism. One conclusion was that, in this group, interpretation of pressure-flow data using the nomogram of Abrams and Griffiths (see Chapter 14) revealed a significantly better subjective outcome for surgery in patients classified as *obstructed* than in those classified as *unobstructed* (93.1% versus 77.8%, $p < .02$). Others have also demonstrated better outcomes for surgery in urodynamically obstructed men than in those with no obstruction.

Successful treatment of BPO by prostatectomy is generally correlated with a reduction in the detrusor pressure ($P_{DET}$). The corresponding detrusor pressure at maximum flow ($P_{DET}$ at $Q_{MAX}$) and the peak flow rate ($Q_{MAX}$) are the most common and most important pressure-flow variables reported. Consideration of the entire pressure-flow plot or other complex mathematical manipulations and graphic representation may, in fact, prove to be more accurate and informative ways of looking at this relationship and may narrow further the diagnostic grey zone between BOO and decreased detrusor function. The problem is that there is not just one such program, but a number of them, with intense competition among their creators in the literature.

## SYMPTOMATIC VERSUS URODYNAMIC IMPROVEMENT

The data from pressure-flow studies can be reported either as raw changes in individual parameters (e.g., $Q_{MAX}$, $P_{DET}$, $P_{DET}$ at $Q_{MAX}$), as a change in category or number designating the grade or severity of obstruction, or by a visual demonstration of change on the nomogram itself. Aside from the utility (or nonutility) of these measurements in assessing the outcome of BPH treatment, a **global question referable to these studies seems to be whether the evaluation of the average older man with LUTS is more likely to lead to a better treatment outcome if urodynamic studies are performed.** In other words, can urodynamic studies predict the outcome of various treatments for LUTS, including watchful waiting? The critical question, when considering a given analysis of pressure-flow data, is: Are patients with LUTS in whom treatment in the form of outlet ablation fails the same as those whose detrusor contractility is judged ineffective by the criteria under consideration? If the answer to this question is no, then the relevance of the analysis is in question, unless it can predict which patients will worsen or which patients will have undesirable sequelae, or it can predict which modalities are apt to be more successful in treatment than others. In our opinion, we who perform urodynamics have done a remarkably poor job of looking into this aspect of outcome analysis.

One final consideration should be mentioned — a seeming dissociation that may occur between symptomatic and urodynamic improvement. This has been most noticeable in data concerning pharmacologic agents. The fact that symptomatic improvement occurs that is seemingly out of proportion to the amount of urodynamic improvement may, in fact, indicate that a given treatment is not equal to the current gold standard of prostatectomy or that the results will be of shorter duration. However, **one important**

**possibility to consider is that the actual symptoms which we will attribute to BPO have much less to do with urodynamically defined obstruction than is thought, and their relief with these other types of treatment has to do more with the correction of some ill-defined mechanism within the prostate and/or prostatic urethra that is not directly related to the amount of mechanical obstruction. Alternatively, it may not be necessary to reduce outlet obstruction by the amount achievable by prostatectomy to significantly improve symptomatology and prevent bladder or upper tract deterioration.**

## The Natural History of BPH and its Alteration

Although LUTS due to BPO may be progressive over time, spontaneous improvement can occur in an untreated patient, and thus the course may be highly variable. Combining data from a number of reports of the natural history of untreated LUTS/BPO, one can conclude that over a 1- to 5-year period, approximately 15% to 30% of patients with clinical BPH will experience subjective improvement, 15% to 55% will have no change, and 15% to 50% will experience some worsening in their symptomatology. Data suggest that over 3 to 5 years 15% to 25% of patients will show an increase in flow rates, 15% will have no change, and 60% to 70% will have some worsening. Placebo responses of 20% to 40% have consistently been reported over the years for drug therapy.

Although BPH is rarely life threatening, it is generally considered to be a slowly progressive disease. Although many patients may do perfectly well with watchful waiting over long periods of time, the natural history of the disease can include undesirable outcomes. More recently, attention has been focused not only on evaluating the acute positive effects of treatment but on stabilizing symptoms, reversing the natural progression of BPH, and avoiding acute or undesirable events. The outcome measures recorded generally include (1) progression of symptoms, or signs, or both; (2) the occurrence of acute urinary retention; and (3) the need for surgical intervention. Progression can be measured in terms of any of the parameters used to assess outcome acutely or subacutely. A matched control group is obviously valuable in this regard because the use of historical control subjects is less than ideal. Acute urinary retention is probably the event most feared by men with BPH. Reported occurrences range from 0.004 to 0.13 episodes per person-year, with a 10-year cumulative incidence rate ranging from 4% to 73%. Others report the incidence of retention in 3 years to be 2.9% and cite incidences in the literature as low as 2% in 5 years and as high as 35% in 3 years. Progression to the point of requiring surgical intervention is an obvious undesirable outcome, but little data are available regarding the incidence of this outcome, especially because the definitions of surgery and the indications and triggers for different types of "make a hole" therapy other than prostatectomy are continually changing.

## Evaluation of LUTS Suspected to Be Due to BPH

The essentials of our initial evaluation include history, digital rectal and focused physical examinations, urinalysis, urine cytology in those with significant irritative symptoms, serum creatinine, renal ultrasound if creatinine is abnormal, and a standardized symptom assessment, such as the American Urological Association Symptom Score (AUASS) or International Prostate Symptom Score (IPSS) (Figure 15-2). **Currently no absolute consensus exists as to routine prostate-specific antigen (PSA) measurement in men with LUTS. PSA can be useful for two reasons: prostate cancer screening and as a parameter for prognostic value for BPH progression and response to treatment.** Prostate cancer screening is addressed in Chapter 16. **PSA is a surrogate for prostate volume in the absence of cancer and a predictor of the risk of acute urinary retention and the ultimate need for surgery in men with LUTS secondary to BPO.** In any case the benefits and risks of PSA measurement, including the issues of false negative and positive results, should be discussed with the patient. The U.S. Preventive Services Task Force issued a recommendation against PSA-based screening for prostate cancer whereas the AUA guideline recommended shared decision making for men age 55 to 69 years who are considering PSA screening, and proceeding based on a man's values and preferences.

Men who do not have absolute or near-absolute indications for treatment (see the following discussion), and have an AUASS of less than or equal to 7 (mild symptoms) do not need further

**AUA Symptom Index (range from 0 to 35 points).**

| | NOT AT ALL | LESS THAN 1 TIME IN 5 | LESS THAN HALF THE TIME | ABOUT HALF THE TIME | MORE THAN HALF THE TIME | ALMOST ALWAYS |
|---|---|---|---|---|---|---|
| 1. Over the last month how often have you had a sensation of not emptying your bladder completely after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. Over the last month, how often have you had to urinate again less than 2 hours after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. Over the last month, how often have you found you stopped and started again several times while urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Over the last month, how often have you found it difficult to postpone urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Over the last month, how often have you had a weak stream while urinating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. Over the last month, how often have you had to push or strain to begin urinating? | 0 | 1 | 2 | 3 | 4 | 5 |

A

**FIGURE 15-2 American Urological Association (AUA) Symptom Index for benign prostatic hyperplasia.** (From Hanno P, Malkowicz SB, Wein A, editors: *Benign prostatic hyperplasia, clinical manual of urology,* New York, 2001, McGraw Hill, T15-2, pp 389–90.)

|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| 7. Over the last month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? | 0, none | 1 time | 2 times | 3 times | 4 times | 5 or more times |

AUA symptom index score: 0−7 mild; 8−18 moderate; 19−35 severe symptoms.

TOTAL ☐

QUALITY OF LIFE DUE TO URINARY SYSTOMS

|  | DELIGHTED | PLEASED | MOSTLY SATISFIED | MIXED ABOUT EQUALLY SATISFIED AND DISSATISFIED | MOSTLY DISSATISFIED | UNHAPPY | TERRIBLE |
|---|---|---|---|---|---|---|---|
| 1. If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |

QUALITY OF LIFE ASSESSMENT INDEX (QOL) =

B. Quality of life assessment recommended by the World Health Organization.

B

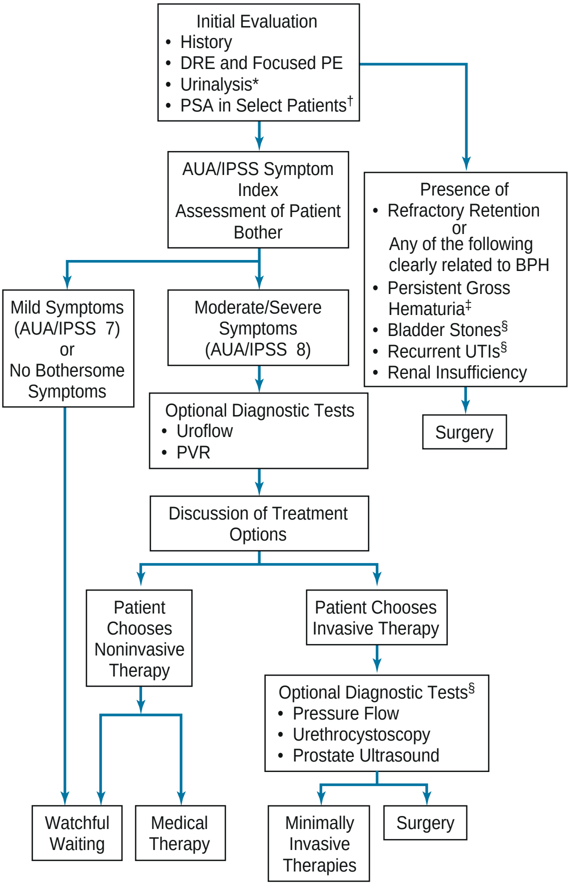
FIGURE 15-2—Cont'd American Urological Association (AUA) Symptom Index for benign prostatic hyperplasia.

evaluation or active treatment but should be followed on a watchful waiting program. In patients with more severe symptoms or who are being considered for active treatment, urodynamics may be desirable. The simplest of these, flowmetry and residual urine volume, are now considered optional in primary management by the AUA Practice Guidelines Committee and the 6th International Consultation on BPH. We consider endoscopic examination of the lower urinary tract to be reasonable if other lower urinary tract pathology is suspected or prior to invasive treatment when the choice of treatment or changes of success or failure depends on the anatomic configuration and/or intraurethral size of the prostate. Algorithms from the AUA Guidelines Committee and the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases are seen in Figures 15-3 and 15-4.

## SYMPTOMS AND SYMPTOM SCORES

Symptoms have classically formed the initial database on which to formulate evaluation of potential outlet obstruction, indications for active treatment, and evaluation of the results of treatment. Symptom quantitation is difficult, and meaningful comparison of symptoms before and after treatment is even harder. The concept of a symptom score or severity table for BPH was first developed by an ad hoc group formed by the Food and Drug Administration (FDA) in 1975; the initial recommendations were published in 1977. Investigators have evaluated every factor imaginable with such scoring tables, eliminating some symptoms and adding others, changing the weights and definitions of the severity of various symptoms, considering some symptoms separately, or dividing the symptoms into storage and voiding groups. **There is generally no provision in a symptom score for considering what actually changed most recently to bring the patient to the physician, what is in fact most annoying to the patient, and what he wants corrected most, or what effect the overall symptom complex, or any one symptom, has on his quality of life, general activities of daily living, or any activity in particular such as sexual activity.**

Through its original Measurement Committee, the AUA formulated indices that address many of the issues relevant to symptom scores and produced a symptom index that has become widely utilized (see Figure 15-2). **This index correlates**


Initial Evaluation
• History
• DRE and Focused PE
• Urinalysis*
• PSA in Select Patients†
AUA/IPSS Symptom Index
Assessment of Patient Bother
Presence of
• Refractory Retention
or
Any of the following clearly related to BPH
• Persistent Gross Hematuria‡
• Bladder Stones§
• Recurrent UTIs§
• Renal Insufficiency
Surgery
Mild Symptoms (AUA/IPSS 7) or No Bothersome Symptoms
Moderate/Severe Symptoms (AUA/IPSS 8)
Optional Diagnostic Tests
• Uroflow
• PVR
Discussion of Treatment Options
Patient Chooses Noninvasive Therapy
Patient Chooses Invasive Therapy
Optional Diagnostic Tests§
• Pressure Flow
• Urethrocystoscopy
• Prostate Ultrasound
Watchful Waiting
Medical Therapy
Minimally Invasive Therapies
Surgery

*In patients with clinically significant prostatic bleeding, a course of a 5α-reductase inhibitor may be used. If bleeding persists, tissue ablative surgery is indicated.

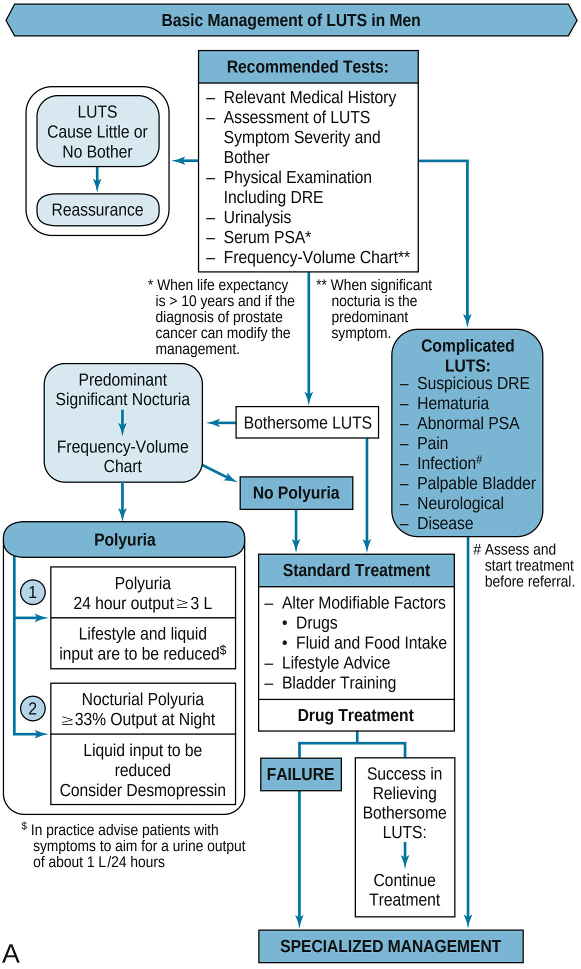
[†] Patients with at least a 10-year life expectancy for whom knowledge of the presence of prostate cancer would change management or patients for whom the PSA measurement may change the management of voiding symptoms.

[‡] After exhausting other therapeutic options as discussed in detail in the text.

[§] Some diagnostic tests are used in predicting response to therapy. Pressure-flow studies are most useful in men prior to surgery.

AUA, American Urological Association; DRE, digital rectal exam; IPSS, International Prostate Symptom Score; PE, physical exam; PSA, prostate-specific antigen; PVR, post-void residual urine; UTI, urinary tract infection.

**FIGURE 15-3 AUA Practice Guidelines Committee algorithm for benign prostatic hyperplasia (BPH) diagnosis and treatment.** (From McVary KT, Roehrborn CG, Avins AL, et al: *Update on AUA guidelines for the management of benign prostatic hyperplasia. J Urol* 185:1793–1803, 2011.


Basic Management of LUTS in Men
Recommended Tests:
– Relevant Medical History
– Assessment of LUTS Symptom Severity and Bother
– Physical Examination Including DRE
– Urinalysis
– Serum PSA*
– Frequency-Volume Chart**
LUTS Cause Little or No Bother
Reassurance
Complicated LUTS:
– Suspicious DRE
– Hematuria
– Abnormal PSA
– Pain
– Infection#
– Palpable Bladder
– Neurological
– Disease
Predominant Significant Nocturia
Frequency-Volume Chart
Bothersome LUTS
No Polyuria
Polyuria
1
Polyuria 24 hour output ≥ 3 L
Lifestyle and liquid input are to be reduced$
2
Nocturial Polyuria ≥33% Output at Night
Liquid input to be reduced Consider Desmopressin
Standard Treatment
– Alter Modifiable Factors
• Drugs
• Fluid and Food Intake
– Lifestyle Advice
– Bladder Training
Drug Treatment
FAILURE
Success in Relieving Bothersome LUTS:
Continue Treatment
SPECIALIZED MANAGEMENT
A

* When life expectancy is > 10 years and if the diagnosis of prostate cancer can modify the management.

** When significant nocturia is the predominant symptom.

# Assess and start treatment before referral.

$ In practice advise patients with symptoms to aim for a urine output of about 1 L/24 hours

FIGURE 15-4 Algorithms for basic **(A)** and specialization

*(Continued)*

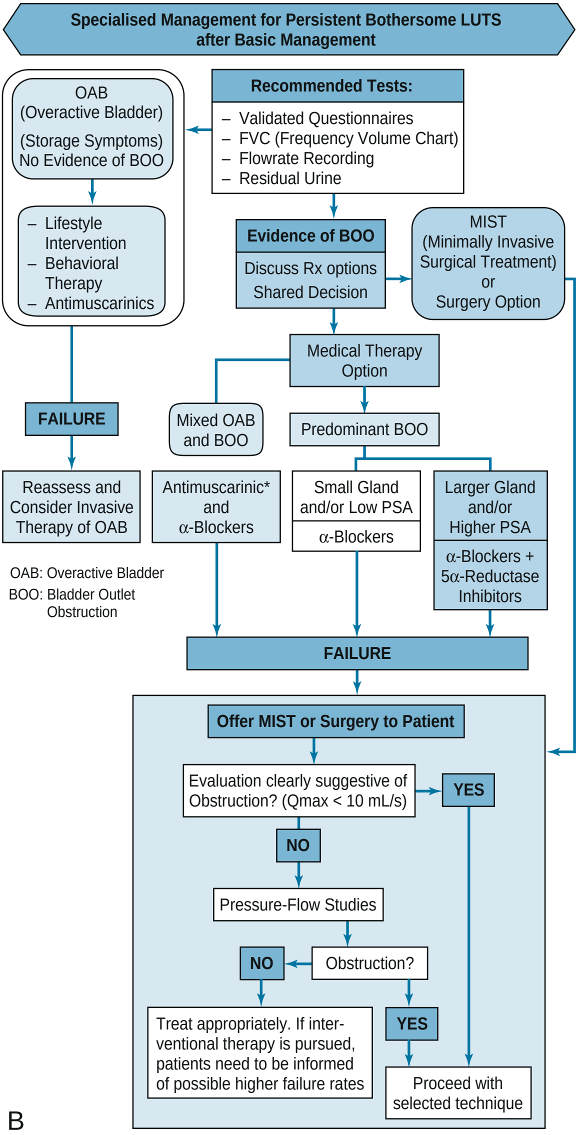

Specialised Management for Persistent Bothersome LUTS after Basic Management
OAB (Overactive Bladder)
(Storage Symptoms) No Evidence of BOO
– Lifestyle Intervention
– Behavioral Therapy
– Antimuscarinics
Recommended Tests:
– Validated Questionnaires
– FVC (Frequency Volume Chart)
– Flowrate Recording
– Residual Urine
Evidence of BOO
Discuss Rx options
Shared Decision
MIST (Minimally Invasive Surgical Treatment) or Surgery Option
Medical Therapy Option
FAILURE
Mixed OAB and BOO
Predominant BOO
Reassess and Consider Invasive Therapy of OAB
Antimuscarinic* and α-Blockers
Small Gland and/or Low PSA
α-Blockers
Larger Gland and/or Higher PSA
α-Blockers + 5α-Reductase Inhibitors
OAB: Overactive Bladder
BOO: Bladder Outlet Obstruction
FAILURE
Offer MIST or Surgery to Patient
Evaluation clearly suggestive of Obstruction? (Qmax < 10 mL/s)
YES
NO
Pressure-Flow Studies
NO
Obstruction?
YES
Treat appropriately. If interventional therapy is pursued, patients need to be informed of possible higher failure rates
Proceed with selected technique
B

**FIGURE 15-4—Cont'd (B) management of lower urinary tract symptoms (LUTS) in men.** (From the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases.)

**highly with the global rating by a subject of the magnitude of urinary problems attributed to BPH and has been reported to satisfy the requirements of validity, reliability, and responsiveness.** The WHO Consultation on BPH has adopted this index, and in this context, it is referred to as the *International Prostate Symptom Score (IPSS)*. **This measure of voiding symptoms is useful to ascertain symptom severity and treatment of response, or change over time without treatment.**

The AUASS/IPSS was originally introduced in 1992 as a symptom index specifically designed for what was called *BPH* at that time. In the years that followed, the questionnaires were administered to samples of men and women, however, and it became obvious that there is **indeed a lack of specificity for LUTS attributed to BPO/BPE. The AUASS/IPSS is neither gender specific nor disease specific because symptomatologies found in men and women are similar.** This argues for an age- or detrusor-related, rather than an obstruction-related, etiology of LUTS in at least a substantial portion of patients.

The AUASS/IPSS does not make the diagnosis of BPH, and it cannot be used to screen for BPH. A variety of primary and secondary bladder abnormalities and nonprostatic causes of obstruction can produce similar symptoms and high symptom scores. In our practice, some of the highest scores are generated by women with filling/storage LUTS. **AUASS/IPSS does not correlate with or predict urodynamically documented BOO. Bothersomeness and effect on the quality of life are not addressed by the AUA questionnaire.** Jerry Blaivas has questioned the accepted statements that the purpose of the AUASS is to quantify severity of disease, document response to therapy, assess patient symptoms, follow the patient with time to determine disease progression, and follow comparison of the effectiveness of various interventions. He lists four reasons why, in his opinion, the AUASS is not a good tool for accomplishing these purposes:

1. Undue emphasis is placed on emptying/voiding compared with filling/storage symptoms. In most series on LUTS in older men, urinary frequency and nocturia are the most common symptoms, and coupled with urge and urge incontinence, they seem to be the most troublesome. Only three of the seven questions relate to these symptoms. Urgency incontinence, which most would consider the most bothersome symptom, is not mentioned.

2. No means exists for quantitating how badly the symptoms bother the patient. An example cited is that a man who voids every half hour during the day, has urgency and urge incontinence half of the time, and gets up three times a night to void scores only 11 of 35 points, yet has severe symptoms. A man who voids three times daily, hesitates, stops and starts, and has a weak stream and sensation of incomplete emptying but no nocturia, urgency, or incontinence scores 20 of 35 points, even if he empties completely, yet has mild to moderate symptoms.
3. The symptom score does not consider the possibility that urinary frequency and nocturia may not reflect any dysfunction or may not be related to the lower urinary tract because many persons void frequently by habit or by choice and do not consider daytime frequency or nocturia to be a symptom.
4. Changes in the symptom score are not necessarily a good measure of therapeutic efficacy because treatment of the most bothersome symptoms may be diluted by the response of symptoms that cause relatively no bother. An example cited is that in many of the original studies on drug treatment of BPH there was no effect whatever of drug versus placebo on the two most troublesome symptoms (nocturia and frequency) and yet there was a statistically significant effect on the overall symptom score.

Change in symptom score is currently the most featured data in any clinical trial but what constitutes a significant change may be viewed differently by patient, investigator, gatekeeper or specialty physician, statistician, manufacturer, and the FDA. In the original publication about the AUASS, the index was noted to decrease from a preoperative mean of 17.6 to 7.1 in 4 weeks after prostatectomy and to 5 at 3 months. (Results of symptom scores can be reported in terms of absolute change or percent change from the pretreatment value.) The higher the pretreatment symptom score, the lower the percent change of a given absolute change. To compare symptom score changes, either absolute numbers or percentages, between groups, the pretreatment symptom scores clearly must be about the same.

## QUALITY OF LIFE INDICES

Perhaps the softest, but maybe the most important, outcome measure to gauge the overall effect of clinical BPH on an individual and the efficacy of treatment for BPH is quality of life. **Most men seek treatment for BPH because of the bothersome nature of their symptoms that affect the quality of their lives.** Symptom severity does not necessarily correlate with bothersomeness or quality-of-life indices. No consensus has been reached as to the optimal tool to record and compare disease-specific quality of life measures in patients with LUTS.

One question on the quality-of-life issue has been included by the International Consensus Committee to assess the impact of symptoms on quality of life in clinical practice (see Figure 15-2). This has been a consistent recommendation since the first WHO consultation on BPH in 1991. Although the Committee recognized that this single question could not capture the global impact of LUTS on quality of life, it was believed that this might serve as a valuable starting point for a physician-patient conversation concerning this issue.

## Indications for Treatment

Indications for **surgery** have varied widely over time, and the current climate is much more conservative than existed 10 to 20 years ago. **Certain absolute or near-absolute indications exist;** they are refractory or repeated urinary retention, related azotemia, significant recurrent gross hematuria, related recurrent or residual infection, bladder calculi, and large related bladder diverticula. All of these assume that the bladder is indeed contractile. In our opinion, a large residual urine volume that is increasing can also be considered an indication.

Without an absolute or near-absolute indication, or combinations of these, the bothersome nature of the symptomatology is generally what prompts the patient to request, or the physician to suggest, treatment. Pathologic urodynamic findings may certainly be influential as well. Once the option of treatment is chosen, the risks and benefits of all applicable modalities must be discussed with the patient, and the patient must ultimately decide among these. General medical status and comorbid conditions may significantly influence this decision. **In general, the more definitive the expectation of a positive outcome is, the more invasive the procedure and the greater the risk.** The term *watchful waiting* has replaced *no treatment*. Ideally each patient would be presented with a chart or other informational medium that describes each possible accepted treatment in terms of the expected likelihood of improvement, the magnitude of improvement, the likelihood of side effects (incontinence, impotence, retrograde ejaculation, and others), and the incidence of reoperation (if a procedure).

## Treatment of BPH and Related Entities

The treatment options are summarized in Table 15-2. The natural history determines the results that can be expected from watchful waiting. It is clear that symptoms do tend to wax and wane and that a substantial number of men will have at least short-term stability or improvement of symptoms. The literature would suggest that, at least over a 5-year period, more than 50% of patients have either improved or have exhibited no change on the basis of subjective criteria. But clinical progression, which can include worsening of symptom score, acute urinary retention, need for invasive surgical treatment, renal insufficiency, and recurrent UTI, does develop and varies based on certain factors, including age, severity of symptom score, PSA, and prostate size. Development of urodynamic parameters to predict those patients who will worsen is clearly of paramount importance. The most commonly used, but not all, therapies are discussed.

### ASSESSING THE RESULTS OF TREATMENT

The outcome measures utilized to assess the results of treatment are seen in Table 15-3. Symptom scores and urodynamic parameters are most commonly used. Quality-of-life improvement and alteration of natural history are currently rarely utilized, an unfortunate state of affairs. It must be recognized, however, that different segments of the population will have different priorities and orientations and may draw different conclusions regarding relative value or efficacy from the same set of outcomes (Table 15-4).

### WATCHFUL WAITING

The AUA guideline on BPH issued a standard recommendation that states for patients with mild symptoms of LUTS secondary to BPH (AUASS score less than 8) and patients with moderate or severe symptoms (AUASS 8 or greater) who are not bothered by their LUTS should be managed using a strategy of watchful

TABLE 15-2 **Treatment Options for Clinical BPH**

- Watchful waiting (observation)
- Pharmacologic
  - Reducing prostate smooth-muscle tone (the dynamic component)
  - Alpha-1 adrenergic antagonists
  - Reducing prostate bulk (the static component primarily)
- Estrogen
  - LHRH agonists/antagonists
  - 5-alpha-reductase inhibitors
  - Antiandrogens
  - Aromatase inhibitors
  - Growth factor inhibitors (theoretical)
- Unknown mechanisms
  - Phytotherapy
  - Other
- Mechanical and surgical
  - Prostatic urethral stents
  - TUMT
  - Transurethral water-induced thermotherapy
- Interstitial therapy
  - TUNA
  - Laser energy
  - High-intensity focused ultrasound
- Ethanol injection
  - Transurethral resection and incision by:
    - Laser (laser TURP, TUIBN-P)
- Electrosurgery (TURP, TUIBN-P)
- Electrovaporization (TUVP)
- Ultrasound aspiration
  - Open prostatectomy

*LHRH,* Luteinizing hormone releasing hormone; *TUMT,* transurethral microwave thermotherapy; *TUNA,* transurethral needle ablution; *TURP,* transurethral prostatectomy; *TUIBN-P,* transurethral incision bladder neck-prostate; *TUVP,* transurethral vaporization of prostate.

waiting. This is a management strategy in which a patient is monitored by his physician but receives no active treatment for BPH. **The rationale for this lies in the fact that the progression of symptoms or deterioration of quality of life occurs in only a portion of men, and treatment intervention is still effective, even when delayed.** The natural history of BPH and the impact of watchful waiting can be seen in the Veterans Administration Cooperative Study that randomized men with moderate symptoms to TURP

TABLE 15-3 **Outcome Measures to Assess the Results of Treatment for Benign Prostatic Hyperplasia and Related Entities**

| |
|---|
| Symptoms and symptom scores |
| Quality-of-life indices |
| Correction of undesirable sequelae (e.g., azotemia) |
| Urodynamic indices |
| Size (for bulk-reducing therapy) |
| Alteration of natural history |
| Adverse effects |
| Cost and cost-effectiveness |

TABLE 15-4 **Populations with Different Viewpoints on Evaluation of Outcomes Following Any Type of Treatment**

| |
|---|
| Patient |
| Family |
| Treater |
| Referrer |
| Friend |
| Manufacturer |
| Competitor |
| Person in the street |
| Agency for Health Care Policy and Research |
| Food and Drug Administration (FDA) |

versus watchful waiting. During 3 years of follow-up, 17% of the watchful-waiting group had treatment failure (defined as acute urinary retention, high postvoid residual urine, or high symptom score) versus 8.2% in the TURP group. The Medical Therapy of Prostate Symptoms (MTOPS) trial demonstrated a similar failure rate in the placebo arm and of which age (> 62 years), larger prostate (> 31 g) and higher baseline PSA values (> 1.6 mg/dL) correlated with progression. While helpful to predict risk, these factors should not be used as sole determinants of the need for active therapy.

## ALPHA-ADRENERGIC ANTAGONISTS

Pharmacologic studies and receptor cloning have identified at least three alpha-1 adrenergic receptor subtypes in the lower urinary tract: alpha-1$_a$, alpha-1$_b$, and alpha-1$_d$. In the prostate, alpha-1$_a$ receptors are found predominantly in the stroma, alpha-1$_b$ in the glandular epithelium, and the alpha-$1_d$ in stroma and blood vessels. The alpha-$1_a$ subtype is the predominant one (about 70%) in stromal tissue. The alpha receptors are found also in the smooth muscle of the bladder base and proximal urethra and in the spinal cord and ganglia as well. The extraprostatic sites of alpha receptors and the lack of absolute receptor or organ selectivity account for their side effects when used for the treatment of LUTS. **The beneficial effects of alpha-blockers in the treatment of BPH are assumed primarily to result from a direct antagonism of alpha-adrenergic–induced tone in the stromal smooth muscle, resulting in a decrease in outlet resistance.**

Some of the history of the development of the use of alpha-blockers for the male LUTS patient can be found in Chapter 14. Commonly used preparations now include alfuzosin, doxazosin, terazosin (once daily), and tamsulosin (once daily). **The percentage of improvement in the total symptom score with these agents ranges from 30% to 45%, with a placebo effect of 10% to 30%. The improvement in maximum flow varies from 15% to 30%, with placebo showing 5% to 15%. It should be noted that numerically these translate into relatively small increments. Potential side effects include dizziness, asthenia, orthostatic hypotension, nasal congestion, and abnormal ejaculation.** Sexual function is complex and is frequently reduced in patients with LUTS/BPH. Alpha-blockers lack major effects on sexual desire and inconsistent data on effects on erectile function but is demonstrated in the domain of ejaculatory dysfunction with rates as high as 28% in the case for tamsulosin. But claims abound as to superiority of individual products. The AUA guidelines committee concluded that the alpha-blockers mentioned previously are appropriate treatment options for patients with LUTS secondary to BPH and that all four agents had equal clinical effectiveness with slight differences in the adverse event profiles. Also despite the *in vitro* specificity of the available drugs, it does not imply an advantage for the improvement of LUTS or the minimization of side effects. Acceptable head-to-head trials are scarce.

## 5-ALPHA REDUCTASE INHIBITORS

The rationale for the use of 5-alpha-reductase inhibitors (5αRI) is that the embryonic development of the prostate is dependent on DHT, to which T is converted by the enzyme 5αR. Both T and

DHT bind to the androgen receptor, although DHT does so with greater affinity and is considered the more potent of the two. The ligand-receptor complex initiates transcription and translation, thus promoting cellular growth and contributing to the condition of BPH. **Two isoenzymes exist. Type 2 is found mainly in the prostate, and type 1 in extraprostatic tissues. Finasteride is a competitive type 2 inhibitor; dutasteride inhibits both types 1 and 2 5αR.** Finasteride reduces serum DHT by about 70%, prostate DHT by 80% to 90%, and dutasteride reduces serum DHT by more than 90%. Finasteride does not reduce DHT levels to castrate levels because circulating T is converted to DHT by type 1 isoenzymes that exist extraprostatically. This reduction results in an increase in apoptosis and atrophy and generally shrinkage of the gland ranging from 15% to 25% at 6 months. This atrophy is most pronounced in the glandular epithelial component of the prostate, which is the source of the production and release of PSA and, as a result, is responsible for the approximately **50% decrease in serum PSA.** Although the number of clinical trials with finasteride is much greater, most agree that clinical efficacy seems comparable at this point: volume reduction of 18% to 26% (placebo –2 to +14), IPSS reduction of 3.3 to 4.5 (placebo 1.3 to 2.3), and peak flow increase of 1.9 to 2.2 (placebo 0.2 to 0.6). **Both are reported to decrease the long-term risk of acute urinary retention and the need for surgery by up to 50% to 60% in patients with enlarged prostates (baseline numbers were, however, small). These benefits are seen primarily in men with enlarged prostates (over 30 to 40 cc). Side effects include decreased libido, ejaculatory disorders, and ED, all with a reported incidence of 5% to 6% and reversible on discontinuation** of therapy (data primarily from finasteride studies). The two agents have not been directly compared specifically with respect to efficacy and tolerability.

## COMBINED THERAPY

**Is combination therapy (alpha-blocker plus 5αRI) more effective than either alone? A Veterans Administration Cooperative Study** by Lepor et al compared placebo, finasteride, terazosin, and finasteride plus terazosin. The mean group differences for all patients between finasteride and placebo were not statistically significant for the AUA symptom index, symptom problem index, BPH impact index, and peak flow rate. The changes for terazosin were significant versus placebo and versus finasteride. The group mean differences between combination therapy and terazosin for all measures other than prostate volume were significantly in favor of terazosin. The volume decrease was 20% in their finasteride and combination groups. The AUASS improvement was 2.6 units for placebo, 3.2 for finasteride, 6.6 for terazosin, and 6.2 for the combination; peak flow rate change was 1.4, 1.6, 2.7, and 3.2 mL/sec, respectively. Finasteride supporters argue that the apparent lack of efficacy in this study was due to a relatively small mean prostate volume in the population studied. For the men with volumes larger than 50 mL, there was a mean increase in $Q_{MAX}$ of 2.5 mL/sec and a mean decrease in AUASS of 2.9, both significantly different from those of comparable men in the placebo group.

The **Medical Therapy of Prostate Symptoms** study looked at the question of whether long-term therapy of BPH with placebo, doxazosin, finasteride, or doxazosin plus finasteride would prevent or delay disease progression, which was defined as a four-point rise in AUASS, 50% increase in baseline creatinine, AUR, two or more UTIs within 1 year, urosepsis due to BOO, or socially unacceptable incontinence. **Based partly on the result of this study, the AUA guideline committee issued an option statement that combination therapy is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate-specific antigen level as a proxy for volume, and/or enlargement on digital rectal examination (DRE).** Combination therapy appeared more effective than alpha-blocker monotherapy in relieving and preventing the progression of symptoms. **The overall risk of progression was reduced** by 39% for doxazosin (D), 34% for finasteride (F), and 67% for a combination. The risk of retention was reduced by 31% for D, 67% for F, and 79% for D + F. **The risk of surgery was reduced by 64% for F and 67% for F + D. Doxazosin alone did not reduce the risk of surgery over placebo. AUASS and $Q_{MAX}$ improved significantly more in the combination therapy group compared with the monotherapy groups, whereas adverse events were similar across treatment groups to previously reported studies. Patients more likely to benefit are those with larger prostates and higher non–cancer-related PSA values,** although absolute thresholds are yet uncertain.

The CombAT (Combination of Avodart and Tamsulosin) trial randomized approximately 5,000 men to receive tamsulosin 0.4 mg versus dutasteride 0.5 mg versus combination therapy with both. Inclusion criteria required patients to have an IPSS score greater than 12, a PSA between 1.5 and 10 ng/mL, and a prostate volume by TRUS greater than 30 g. The recently published 4-year follow-up data demonstrated, irrespective of baseline subgroup, the incidence of AUR or BPH-related surgery was higher among patients treated with tamsulosin compared with dutasteride and combined therapy and generally the lowest for patients on combined therapy. Across treatment groups, incidence was higher for those with baseline IPSS scores greater than 20, PSA value greater than 3 ng/mL, and prostate volume greater than 40 mL. Clinical progression followed a similar trend with higher rates among men receiving tamsulosin than dutasteride or combined therapy.

## ANTICHOLINERGIC AGENTS

In the human bladder, the muscarinic receptor subtypes M2 and M3 are primarily responsible for bladder contraction. Blockage of this interaction by anticholinergic agents results in reduction in smooth muscle tone and improved symptomatology of overactive bladder (OAB). An overlap exists between the LUTS secondary to BPH and those of OAB such that the AUA guideline issued its use as an option and stated it is an appropriate and effective alternative for the management of LUTS secondary to BPH in men without an elevated PVR and when LUTS are predominately irritative. In a meta-analysis that assessed the safety and efficacy of anticholinergic agents either as monotherapy or in combination with an alpha-blocker in men with LUTS related to BPH, minimal changes were reported in $Q_{MAX}$ and IPSS scores, a minimal increase in PVR, and no convincing increase in AUR rates.

## COMPLIMENTARY AND ALTERNATIVE MEDICINE

Complimentary and alternative medicine (CAM) for the treatment of LUTS generally consists of phytotherapeutic preparations in the form of dietary supplements that include extracts of saw palmetto plant (Serenoa repens) and stinging nettle (Urtica dioica), among others. The mechanism of action is unknown but may be related to modulation on prostaglandin synthesis or alterations in growth factor-induced proliferation. Most of these preparations involve various components extracted by various techniques, yielding different concentrations and complicating their comparison among different manufacturers. Additionally, these manufacturers are exempted from prospective oversight from the FDA, and thus the quality and purity of these supplements are not rigorously monitored. But they have great appeal to patients because they are assumed to be "natural" products and are available over the counter. Use varies according to the severity of the symptoms, with CAM being given to patients with the lowest IPSS and combination therapy with alpha-blocker and 5αRI for those with the highest IPSS. The recent AUA guidelines issued a consensus statement that no dietary supplement or other nonconventional therapy is recommended for the management of LUTS secondary to BPH, either due to lack of proven effect or insufficient evidence to offer clear clinical guidance.

## MINIMALLY INVASIVE THERAPIES

Traditional electrocautery, laser, microwave, and radiofrequency energy can be utilized to resect, vaporize, or cause coagulation necrosis of prostatic tissue. At temperatures lower than 45 degrees C, coagulation necrosis of normal tissue does not occur. **Irreversible cellular damage begins to occur above 45 degrees C.** Coagulation can take up to an hour to occur at temperatures minimally above this level. At 60 to 100 degrees C, coagulation is rapid and at 100 degrees C is virtually instantaneous. **At temperatures higher than 100 degrees C, tissue vaporization is produced.**

## TRANSURETHRAL MICROWAVE THERMOTHERAPY (TUMT)

This is the most commonly utilized method of energy ablation in the **office setting.** A large body of literature supports both the efficacy and the very low rate of significant side effects of these therapies. These systems are based on urethral catheters that house a microwave transducer just proximal to the anchoring balloon and thus dwell within the prostate during treatment. Newer systems have evolved to include higher energy levels and concomitant urethral cooling systems to offset these higher energy effects on adjacent tissue. After placement of this catheter and a rectal temperature sensor, **the microwave is activated to heat the prostate adenoma to a target temperature of at least 45 degrees C for an extended period of time** (30 to 45 **minutes**). This causes coagulation necrosis and subsequent reduction in the size of the adenoma allowing for improved peak flow and reduction of symptom score that is durable in one report up to 11 years. **Results are encouraging but still do not match those of transurethral resection of the prostate** (TURP). Systemic review of randomized controlled trials (RCTs) with 540 patients revealed a pool mean $Q_{MAX}$ increase from 7.9 to 13.5 mL/sec after TUMT versus 8.6 to 18.7 mL/sec after TURP. Representative results from studies with follow-up greater than 5 years include an increase in $Q_{max}$ from 6.7 to 11.4 mL/sec and 6.5 to 8.9 mL/sec, and a decrease in IPSS from 21 to 7.4 and 22.5 to 11.9. But conflicting results abound as a result of a heterogenous mix of studies that differ in size, follow-up, outcome measure, and model of TUMT system. Generally, the newer systems appear to have improved efficacy and longer durability but study dropouts can be significant and may suffer from selection bias. Thus results may be misleading if analysis is performed only on these best “responders.” These procedures are performed in the office setting with only local anesthesia via lidocaine jelly. However, many patients initially require an indwelling urethral catheter for a few days postprocedure due to problems with urinary retention caused initially by edema, though this is decreasing as well in the newer systems with a post-TUMT catheterization rate less than 20% in some studies. Additionally, urinary symptoms require 6 to 12 weeks to improve posttreatment. Side effects and complication profiles are generally very low with this form of therapy but generally at the expense of a higher risk of requiring additional BPH treatment compared with TURP.

## TRANSURETHRAL NEEDLE ABLATION OF THE PROSTATE

Transurethral needle ablation of the prostate (TUNA) is also an **office-based procedure in which radiofrequency energy is used to ablate prostatic adenoma.** The system is based on a cystoscopelike device that allows the surgeon to visualize the prostatic urethra and then deploy electrodes into the parenchyma of the prostate that deliver radiofrequency to heat the prostate to 80 to 100 degrees C. Each cycle, lasting about 5 minutes, creates an area of necrosis that is rather small and thus requires multiple lesions to be created in a systematic fashion to debulk the prostate. But the reduction in prostatic volume is less than initially anticipated because the BPH histology is likely replaced with scar, leaving a modest volume reduction. Total treatment times range from 30 to 60 minutes. **Randomized trials have shown effectiveness both subjectively and objectively.** More than 500 patients have been observed for 12 months and had an average $Q_{MAX}$ improvement of 77% and a symptom score improvement of 58%. Durable results were seen at the 5-year follow-up that included a $Q_{MAX}$ change from 8.8 to 13.5 mL/sec and a AUASS change from 20 to 11.7, though these results have to be carefully interpreted because only 28% of the initial study group was available. **The AUA guideline panel concluded, based on these trials, that the symptom improvement is significant and sustained for both TUNA and TURP, but with somewhat greater improvement in the symptom score for TURP.** Side effects are also mild and generally self limited; posttreatment urinary retention occurs at a rate between 13.3% and 41.6%, and irritative voiding symptoms occur in about 40% of patients but generally resolve and last between 1 to 7 days. Sexual dysfunction and stricture are rare, but, as for TUMT, retreatment rates are higher from TUNA than TURP, with 14% of patients who underwent TUNA requiring a reoperation within 2 years.

## SURGICAL PROCEDURES

Surgery represents the most invasive option for the management of LUTS. It is typically performed in the operating room setting, requiring either general or regional anesthesia, and is associated with the greatest risks for morbidity and higher costs. Surgery is appropriate for moderate to severe LUTS, AUR, or other BPH-related complications and is generally reserved for those who have failed medical therapy. Surgical management has evolved from extirpative surgery towards less invasive, endoscopic procedures utilizing laser energy that represent efficacious alternatives with lower perioperative morbidity. This includes a generally shorter postoperative duration of catheterization and length of hospital stay.

## LASER USAGE

The tissue effects of laser energy are produced by the virtually instantaneous attainment of temperatures higher than 60 degrees C to create coagulation necrosis and above 100 degrees C to create vaporization. The types of laser commonly utilized for clinical BPH treatment include potassium titanyl phosphate laser (KTP), a free beam treatment with high energy density to create vaporization without concurrent deep coagulation, and pulsed holmium: yttrium-aluminum-garnet (Ho:YAG), which causes thermomechanical vaporization and can be used as a cutting tool. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is infrequently used, given that its poor absorption by water and body pigments allows for relatively deep tissue penetration. This poor absorption in a fluid medium causes thermal coagulation of the surface tissue and of areas just under the surface. To achieve vaporization, higher energy levels are needed.

## PHOTOSELECTIVE VAPORIZATION OF THE PROSTATE (PVP)

The KTP laser (wavelength 532 nm) is utilized during this procedure. **This wavelength is highly absorbed by oxyhemoglobin, thus allowing efficient tissue vaporization with excellent hemostasis.** A specialized side-firing laser fiber is utilized cystoscopically to focus the energy into the prostate causing vaporization of all vascularized tissue. Representative results from one of the few randomized trials comparing PVP and TURP at 1 year show similar improvement in $Q_{MAX}$ (approximately 115%), 61% versus 53% decrease in IPSS, catheterization time of 13.3 versus 44.7 hours ($p < 0.001$), and a significant decrease in length of hospital stay (1.09 versus 3.6 days, $p < 0.001$). Additionally, costs were reported to be 22% less in the PVP group. Advantages include excellent hemostasis allowing use on anticoagulated patients, no risk of TUR syndrome, and a quick learning curve. Side effects are minimal. Drawbacks include difficulty of resection of very large glands (greater than 80 gm).

## HOLMIUM LASER ENUCLEATION OF THE PROSTATE (HoLEP)

The addition of high-powered holmium lasers (80 to 100 W) has enabled urologists to perform prostate resection. Holmium energy (wavelength 2120 nm) allows actual resection and debulking of adenoma in a similar fashion to standard TURP. Holmium energy has a minimal depth of penetration (0.4 mm) but divides tissue in a nearly bloodless fashion. **The HoLEP procedure utilizes a continuous-flow resectoscope with an end-firing 550 micron fiber that enables enucleation of the prostate in a fashion similar to open suprapubic prostatectomy. The laser fiber is used to incise the prostate adenoma down to capsule, and then entire lobes of the prostate are enucleated and pushed into the bladder. Once the entire adenoma is resected, a tissue morcellator is used cystoscopically to remove the prostate piecemeal. Significant advantages include excellent hemostasis, results equivalent to standard TURP, no risk of TUR syndrome (saline irrigation), and a shortened hospital stay.** Patients who are fully anticoagulated can be treated using this approach. Generally, the results compare favorably to open prostatectomy in an experienced group; the 5-year follow-up results of a RCT comparing the two for patients with greater than 100 g prostates had similar findings with a mean AUASS of 3 and a mean $Q_{MAX}$ of approximately 24 mL/sec. Late complications and reoperative rates were similar as well. At 7 years of follow-up comparing HoLEP versus TURP in those with a mean TRUS of approximately 70 mL, mean AUASS (8 versus. 10.3) and $Q_{MAX}$ (22 versus 17.8 mL/sec) were similar. While operative time for HoLEP was longer (62.1 versus 33.1 min, $p < 0.001$), the amount of resected tissue (40.4 versus 24.7 g, $p < 0.05$), duration of catheterization (17.7 versus 44.9 hrs, $p < 0.01$) and length of hospital stay (27.6 versus 49.9 hrs, $p < 0.001$) favored the HoLEP group. **Drawbacks are a significant learning curve and a need for a high-power laser and morcellation.**

## HOLMIUM LASER ABLATION OF THE PROSTATE (HoLAP)

The HoLAP procedure is a modification of the HoLEP that also requires a continuous flow resectoscope, high-powered holmium laser, and, instead of an end-firing laser fiber, a side-firing laser fiber. During this procedure, the laser fiber is employed to vaporize the surface tissue of the adenoma via continuous delivery of laser energy. With the minimal depth of penetration of the holmium energy, this approach can be time consuming; however, it does provide bloodless, immediate debulking of adenoma. Single group cohort studies involving HoLAP and TURP indicate that the $Q_{MAX}$ improved in both groups, with improvements sustained at up to 24 months follow-up and similar in both groups. Drawbacks include difficulty in treatment of prostates greater than 80 g in size.

## HOLMIUM LASER RESECTION OF THE PROSTATE (HoLRP)

The HoLRP procedure involves resection of the prostatic adenoma using a holmium laser fiber and a specially adapted resectoscope. Two-year follow-up in a RCT comparing HoLRP with TURP yielded no difference between the two groups in AUASS or $Q_{MAX}$. No recent studies have been published for HoLRP, appearing to have been displaced by HoLEP. The AUA guideline groups these four aforementioned laser therapies together and graded them as an option and as appropriate and effective treatment alternatives to TURP and open prostatectomy in men with moderate to severe LUTS; the guideline says the choice of approach should be based on the patient's presentation anatomy, the surgeon's level of training and experience, and discussion of potential benefits and risks for complications.

## TRANSURETHRAL RESECTION OF THE PROSTATE

**This remains the gold standard of treatment for symptoms of BPH.** This technique uses a resection loop and electrosurgical generator capable of delivering cutting and coagulating current. The lower-voltage, continuous-cutting wave form instantaneously vaporizes a path through the tissue and does not result in significant coagulation. The coagulation current consists of short segments of higher-voltage, lower-current energy, resulting in deeper penetrative heating and hemostasis. **Resection via electrocautery loop by a transurethral route has, on literature review, a 75% to 96% chance of improvement of symptoms, with the degree of improvement 4 on a scale of 4. Modern series reporting risks of TURP have shown significant improvement.** The Veterans Affairs Cooperative Study on TURP remains the most definitive study on the efficacy and safety of TURP. In this RCT comparing TURP with watchful waiting, improvements at the 3-year follow-up were noted for symptom score, $Q_{MAX}$, and multiple quality-of-life measures in favor of TURP. Relative risk of treatment failure was 0.48 favoring TURP. The rate of urinary incontinence was 1% (which was similar to the watchful-waiting group) and an overall decline in sexual function that was identical to the watchful-waiting group. Hemorrhage requiring transfusion occurred in 1%. The incidence of bladder-neck contracture and urethral stricture was 3.2%. Retrograde ejaculation is common and occurs in 50% to 95%. No mention was made of patients suffering from TUR syndrome, **a potentially devastating complication that is caused by intravascular absorption of irrigating fluids. Dilutional hyponatremia and fluid overload can occur leading to bradycardia, neuromuscular dysfunction, seizures, coma, and death. If suspected, immediate treatment with intravenous saline, IV mannitol, and loop diuretics should be instituted.** Additionally, patients can expect to stay in the hospital for 1 to 3 days postsurgery with an indwelling catheter during that time. Newer procedures are being refined to help decrease these risks and morbidity. Bipolar resection of the prostate utilizes a specialized resectoscope loop that incorporates both the active and return electrodes. This design limits the dispersal of current flow and allows for the use of 0.9% sodium chloride as the irrigation fluid. Meta-analysis of RCT that compared the two techniques noted overall poor trial quality and while long-term efficacy evaluation of bipolar TURP was not possible, the occurrence of TUR syndrome and postoperative clot retention was significantly less than for monopolar TURP.

## TRANSURETHRAL ELECTROVAPORIZATION OF THE PROSTATE (TUVP)

This technique that is very similar to TURP involves substitution of the resection loop of the resectoscope with a broad-based, rolling electrode that can be swept over the surface of the prostate while the electrical current is activated. The high-power density that is transmitted literally vaporizes the underlying tissue. This technique requires more time than resection and thus in most studies, prostate size was less than 60 g. TUVP decreases risks of hemorrhage and TUR syndrome because vessels are sealed during vaporization. The desiccated base, however, is less susceptible to further vaporization. No tissue is recovered during the procedure. In the published trials comparing TURP to TUVP, improvements in symptom score and peak flow rates have been demonstrated but generally with no difference between the two treatment groups for up to 1 year of follow-up. Sexual side effects, incontinence rates, stricture, and bladder-neck contracture rates are similar to those following TURP but postoperative duration of catheterization, hospital stay, hematuria, transfusion rate, and retrograde ejaculation were lower for the TUVP group.

## TRANSURETHRAL ELECTROSURGICAL INCISION OF THE BLADDER NECK AND PROSTATE (TUIBN-P)

For patients with smaller prostates (less than 30 g) this procedure involves simply incising through the bladder neck from a point distal to the ureteral orifices to the lateral edge of the verumontanum. The incision(s) can be performed with either electrocautery or holmium laser energy at the 5 or 7 o'clock position or on one side of the midline only. Ideal candidates are those with little lateral lobe hypertrophy, no median lobe hypertrophy, and a high posterior lip of the bladder neck. In suitable candidates, improvement in peak flow rates is approximately the same, global improvement rates slightly less (80% to 95% versus 85% to 100%), retrograde ejaculation much less but can vary based on the number of incisions (0 to 37%), and bladder-neck contracture much less (1%). Impotence has been rarely reported, and incontinence is seen in 0% to 1% of patients. This is certainly an underutilized procedure; based on historical statistics, nearly 80% of patients undergoing TURP in the United States have less than 30 g of tissue resected. A single RCT is available that compared TUIP to TURP in subjects whose prostate was less than 30 g. With 2 years of follow-up, both groups improved significantly in symptom score and peak flow rate, but no difference in outcome was noted between the two groups.

## OPEN PROSTATECTOMY

This increasingly infrequently utilized option for BPH is clearly the most invasive but may still be the treatment of choice for prostates larger than 100 g. This operation, first described by Fuller in 1894, is performed through a lower midline incision and allows complete, intact removal either through the bladder or through the anterior capsule of the prostate. However, the morbidity of the procedure stemming from complications, including retrograde ejaculation, impotence, UTI, transfusion, stricture, incontinence, bladder-neck contracture, ureteral obstruction, and persistent urine leak, makes this operation generally less attractive and thus less often performed. When compared with TURP, open prostatectomy is associated with lower retreatment rates and more complete removal of prostatic adenoma. Recent publications report the viability of laparoscopic and robotic-assisted transvesical prostatectomy. However, this experience is still limited to small case series, but it appears symptom improvement is comparable to the open approach while with significantly less total blood loss, duration of catheterization, and length of hospitalization but at the expense of longer operative time.

It is clear that the age of significant morbidity for treatment for BPH is coming to a close. More data over longer periods of follow-up are necessary to fully describe the natural history and advantages and disadvantages of other methods of therapy including watchful waiting. In the future, patients will likely be presented with a checklist of the advantages and disadvantages of each type of management. The number of surgical and mechanical therapies dictates, however, that no one practitioner will have expertise with all of these, but rather each will have his or her "favorites," based on sound reasoning and results. Patients with minimal to moderate symptoms and bother, who do not have an absolute indication for surgery, will doubtless choose less invasive therapy, at least initially. Minimally invasive therapies offer many patients significant durable relief of BPH-related symptoms as an outpatient with minimal morbidity. Even TURP, the traditional gold standard, with its significant improvement in morbidity over open prostatectomy, is rapidly becoming replaced by less invasive treatments. Even those patients with extremely large prostates may be able to select a laparoscopic approach to prostatectomy in the near future. Finally, it remains to be seen how much, if anything, is "lost" by utilizing those surgical mechanical methods that do not yield tissue for pathologic analysis because prior to the PSA era, approximately 10% to 12% of prostatectomy specimens were found to contain unsuspected cancer. Although this is probably less with the advent of widespread PSA testing, it remains to be seen whether any noticeable delays in the diagnosis of cancer occur and, if so, whether outcome is adversely influenced.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Discuss the varying definition of BPH (microscopic, macroscopic, and clinical) and the epidemiology of each.*
2. *Discuss the origin and meaning of the term LUTS, the subdivisions of LUTS, and their potential etiologies.*
3. *Discuss the typical urodynamic changes seen in moderate to severe bladder outlet obstruction (BBO) secondary to BPH.*
4. *Discuss the outcome measures for evaluating the efficacy of therapy for clinical BPH and their relative importance.*
5. *Discuss the pharmacologic and ablative therapies of clinical BPH, including expected changes in symptom scores and flowmetry.*

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## CHAPTER 16

# Adult Genitourinary Cancer: Prostate and Bladder

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## Prostate Cancer

### GENERAL CONSIDERATIONS

Prostate cancer is the most common cancer in men and the second greatest cause of cancer mortality in men. One in six men will be diagnosed with prostate cancer; however, only one in 36 will die from prostate cancer. Prostate-specific antigen (PSA) screening has led to a dramatic stage shift over the last two decades, with most men currently presenting with low-risk, organ-confined disease. PSA screening has also led to an increase in the detection of indolent prostate cancer as evidenced by the discrepancy between lifetime risk of prostate cancer diagnosis compared to that of prostate cancer mortality. Early detection likely improves outcomes in a subset of men; however, overtreatment of indolent cancer is now recognized as a potential drawback of screening. For those with localized disease, definitive therapy provides excellent oncologic outcomes. For those patients with intermediate or high-risk cancer for whom the risk of disease recurrence after local therapy is significant, combined modality therapy may be beneficial. The nature of biochemical recurrence after local treatment is being better defined, allowing for the stratification of these patients. Treatment of advanced disease has classically been provided through some form of androgen ablation and cytoreductive chemotherapy; however, recent advances in the treatment of locally advanced and metastatic prostate cancer are likely to redefine our treatment paradigms in this patient population moving forward.

## INCIDENCE

**In 2013 there were an estimated 238,590 new cases of prostate cancer and approximately 29,720 cancer-related deaths in the United States.** Worldwide there are approximately 899,000 new cases per year with 258,000 deaths, making it responsible for almost 12% of all new cancers and nearly 6% of cancer deaths. After the rapid increase in detected cases after the introduction of PSA testing, the number of incident cases has decreased to its present level. The death rate from prostate cancer has decreased by approximately 25% in the past decade, yet it cannot be said with certainty at this time that this is the result of earlier detection and therapy.

## PSA SCREENING

PSA screening has been in widespread use in the United States for two decades. While we have definitely noted a stage migration toward that of lower risk, clinically localized disease, the benefit of screening remains controversial. Recently the results of two large randomized PSA screening studies have been reported with conflicting results. The Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial randomized 76,693 men in the United States to receive annual prostate cancer screening versus usual care. **After 7 to 10 years of follow-up, there was no difference in prostate cancer mortality between the screened and unscreened groups.** However, the methodology of this study has been heavily criticized. Notably, there was a significant (53%) contamination rate in the control group in addition to 40% of men undergoing at least one PSA test prior to randomization. Furthermore, the biopsy rate was only approximately 40% in men who were positively screened. The European Randomized Study of Screening for Prostate Cancer (ERSPC) randomized 162,387 men from seven European countries to receive PSA screening versus no screening. **With a mean follow-up of 8.8 years, a 20% relative risk reduction from prostate cancer mortality was reported in the PSA-screened group.** The number needed to screen to prevent one prostate cancer death was 1,410, and the number needed to treat was 48; however, these numbers have proven to be lower with greater follow-up.

The negative findings in the PLCO study, the high number needed to treat in the initial ERSPC study, and the potential morbidity associated with prostate biopsy and definitive treatment led the U.S. Preventive Services Task Force (USPSTF) to recommend against population-based PSA screening for prostate cancer. The USPSTF recommendation has sparked much debate both within and outside of the urologic community. The American Urological Association (AUA) has also recently updated their clinical guidelines on prostate-cancer screening. **The AUA has made the following recommendations:**

1. PSA screening in men under the age of 40 is not recommended.
2. Routine screening in men between the ages of 40 to 54 years at average risk is not recommended.
3. For men 55 to 69 years old, the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1000 and screened over a decade against the known potential harms associated with screening and treatment. For this reason, shared decision making is recommended for men age 55 to 69 years who are considering PSA screening, and proceeding based on the patient's values and preferences.
4. To reduce the harms of screening, a routine screening interval of 2 years or more may be preferred over annual screening in those men who have participated in shared decision making and decided on screening. As compared to annual screening, it is expected that screening intervals of 2 years preserve the majority of benefits and reduced overdiagnosis and false positives.
5. Routine PSA screening is not recommended in any man over age 70 or any man with less than a 10 to 15 year life expectancy.

## EPIDEMIOLOGY

Prostate cancer is distributed in a very uneven manner with regard to race. Black **Americans have the highest mortality rate from this disease, which is also highly prevalent in the Caribbean and Africa.** There is a significant contrast to native Asian men who have the lowest disease incidence and death rate from this condition. Although lower than in other ethnic groups, prostate cancer incidence and disease mortality demonstrate an upward trend in Asian countries. Caucasian men in the United States and Europe have an intermediate rate of disease expression, with the highest incidence rate and disease mortality found in northern Europeans.

1. Age: The autopsy incidence of prostate cancer can be significant by the fourth decade of life and is at least 30% in men older than the age of 50 years and more than 70% by the eighth decade of life. Clinical detection occurs at earlier ages because of increased awareness and more intense disease screening. More significant disease may be found in black Americans at an earlier age.
2. Family history: **A twofold greater risk for developing prostate cancer exists in those individuals with a first-degree relative with prostate cancer.** This climbs to almost ninefold if three first-degree relatives are affected. Risk also exists if second-degree relatives have a diagnosis of prostate cancer. Alterations in specific genes or genetic loci may contribute to the development of disease. Hereditary prostate cancer is usually defined as multiple affected family members and a distribution along several generations. Approximately 20% of patients may have a familial association with another individual with prostate cancer.
3. Geography: Data suggest an inverse relationship between latitude and the incidence of prostate cancer. Northern populations have a greater level of disease, and it is hypothesized that it is related to the lower vitamin D levels secondary to less exposure to ultraviolet radiation. This may also be due to dietary changes or other factors. Native black populations in Zaire have lower levels of prostate cancer compared to ethnic Zairians living in Belgium.

## PATHOLOGY

The proposed pathway from inflammatory atrophy to invasive disease is a working hypothesis under investigation. Evidence for high-grade PIN as a precursor of invasive disease has grown stronger with further genetic and biochemical research. PIN is the proliferation of the acinar epithelium, and high-grade PIN is associated with the subsequent diagnosis of prostate cancer in approximately 25% of patients. Although the natural history of this condition is incompletely defined, patients should be counseled regarding the association between high-grade PIN and prostate

## ETIOLOGY

1. The genetic factors responsible for prostate cancer are being actively investigated. At this time a few candidate prostate cancer genes have been identified, yet the majority of data suggests that subtle changes in several different genes involved in such vital areas as steroid metabolism or detoxification may have an aggregate affect on prostate cancer disposition.
    a. HPC1/RNASEL (1q24–25) and PG1/MSR1 (8p22–23) are potential prostate cancer-specific susceptibility genes, which functionally deal with inflammatory and infectious processes. Their exact roles in cancer etiology are under intense scrutiny. HP1C, which is an autosomal dominant gene, has been reported to have a fairly high penetrance in genetic carriers.
    b. Recently chromosomal rearrangements similar to that seen in certain sarcomas have been identified in prostate tumors. Gene fusions resulting in androgen-driven oncogenic gene products suggest a new method of tumor pathogenesis. This is exemplified in the fusion/rearrangement of TMPRSS2 with ETS transcription factor genes. TMPRSS2-ETS fusion has been identified in up to 50% of PSA-detected tumors. The utility of TMPRSS2-ETS fusions as a prognostic marker is yet to be elucidated but is under investigation.
    c. Androgen receptor CAG repeat length, alterations in SRD5A2 (5-alpha reductase-2), and cytochrome p450 genes associated with steroid metabolism (Cyp 3A4, Cyp 19A1, Cyp 17A1) have some relative impact on prostate cancer susceptibility alone or in concert.
    d. Data suggest that the GSTM1-null phenotype may increase prostate cancer risk in smokers.
2. Androgens: Studies on androgen levels have been conflicting but have suggested higher testosterone levels or dihydrotestosterone/testosterone ratios in black American men. Exposure to androgens at certain developmental time periods is likely critical in prostate cancer carcinogenesis. Mutations or alterations in the androgen receptor (CAG repeats) may also be unequally distributed among individuals in populations, affecting response to testosterone.
3. Diet: High intake of animal fat is associated with increased prostate-cancer risk. Conversely the intake of soy products

(isoflavonoids, phytoestrogens, Bowman-Birk inhibitor) may affect the development and progression of prostate cancer. Migration studies of Asians moving west demonstrate an increase in prostate cancer incidence compared to that of Caucasian populations in the same area. Studies in other tumor systems on vitamin E and selenium showed a one-third to two-third decrease in prostate cancer incidence, respectively. However, studies specifically designed to evaluate the effect of vitamin E and selenium in prostate cancer have not demonstrated a preventative association.

4. Insulin like growth factor (IGF) system. These are peptides similar in structure to proinsulin that modulate proliferation, apoptosis, and tissue repair. IGF-1 and IGF-2 combine with one of six binding proteins (usually IGFBP3). Several studies have demonstrated that elevated serum levels of IGF-1 are associated with a higher risk of prostate cancer. The relative impact of the IGF axis on prostate cancer development or detection is currently unclear.
5. Inflammation: A growing body of investigation suggests that chronic inflammatory processes may play a role in the pathogenesis of prostate cancer. A pathway from normal tissue to proliferative inflammatory atrophy (PIA), to prostatic intraepithelial neoplasia (PIN), with resultant invasive prostate cancer has been proposed.

cancer, and repeat prostate biopsy should be considered within one to three years after an initial diagnosis of high-grade PIN.

1. Adenocarcinoma: The majority of prostate tumors are adenocarcinoma, which develops from the acinar glands. The majority of these arise from the peripheral zone of the prostate gland, yet up to 25% may originate in the central gland from the central and transitional zones.
2. Mucinous variant: If more than 25% of the representative tissue has mucin-containing glands, this designation may be given. It is purported to have an equal or worse outcome than classic adenocarcinoma.
3. Signet cell carcinoma: This is another adenovariant with rapid progression and poor prognosis.
4. Endometrioid or ductal carcinoma: A variant that usually presents at advanced stage with papillary-like growth; ductal carcinoma generally has a poor prognosis.
5. Small cell carcinoma: A neuroendocrine variant of prostate carcinoma, this often presents with normal PSA values. Although the general prognosis is poor, it may respond to platinum-based therapy.
6. Urothelial carcinoma: This may arise from the distal prostatic ducts. It is usually manifest as an extension of primary bladder cancer. Stromal invasion carries a poorer prognosis than ductal infiltration.
7. Prostate sarcoma: This is a very rare tumor, generally designated as leiomyosarcoma. Recent data demonstrate c-kit positive staining in several cases suggesting potential therapy with Gleevec.
8. Hematologic malignancies: Leukemia and lymphoma variants are rare.
9. Metastases: Malignant melanoma, colorectal carcinoma, and pulmonary metastases have been documented.

## GRADING AND STAGING SYSTEM

1. **The Gleason grading system is the standard grading system for prostate adenocarcinoma.** When tumors were diagnosed as incidental findings after transurethral resection of prostate (TURP), lower grade designations were commonly assigned. However, needle biopsy specimens and surgical specimens are usually assigned a grade from 3 to 5. The two most

common patterns are added together to provide a Gleason score with the grade of the most predominant tumor listed first. This provides stratification of score 7 lesions as 3+4 or 4+3, which can have some prognostic implications.

2. Staging is generally designated by the TNM system (Tables 16-1 and 16-2). This provides a general description of tumor extent, yet may not fully represent the degree of tumor volume or the significance or insignificance of microscopic tumor extension beyond the prostatic capsule. Often the designation of organ confinement, extracapsular extension, and the degree of margin positivity, with some sense of the overall tumor volume, better describes lesions that are similar yet might be categorized more divergently.

## SIGNS AND SYMPTOMS

Screen-detected prostate cancers are typically asymptomatic. In more advanced stages, it may be associated with urinary

TABLE 16-1 **TNM Classification**

| TNM 2002 | Histologic Description |
|---|---|
| Tis | Carcinoma in situ |
| Ta | Epithelial confined, usually papillary |
| T1 | Invading lamina propria |
| T2a, b | Invasion of the muscularis propria:<br>2a: superficial invasion<br>2b: deep invasion |
| T3a, b | Perivesical fat invasion:<br>3a: microscopically<br>3b: macroscopically |
| T4a, b | Invasion of contiguous organs:<br>4a: prostate, vagina, uterus<br>4b: pelvic sidewall, abdominal wall |
| NO | No lymph node involvement |
| N1 | Single ≤2 cm |
| N2 | Single >2 cm, ≤5 cm<br>Multiple ≤5 cm |
| N3 | Single or multiple > 5 cm |
| M0 | No distant metastases |
| M1 | Distant metastases |

TABLE 16-2 **TNM Definitions**

| TNM 2002 | Definitions |
|---|---|
| T1 | Tumor an incidental histologic finding |
| T1a | < Gleason score 7<br><5% of tissue resected<br>Tumor an incidental histologic finding |
| T1b | > Gleason score 7<br>>5% of tissue resected |
| T1c | Tumor identified by needle biopsy (e.g., for elevated serum PSA) |
| T2 | Tumor confined within the prostate |
| T2a | Tumor involves one lobe or less |
| T2b | Tumor involves more than one lobe |
| T3 | Tumor extends through and beyond the prostate capsule |
| T3a | Unilateral extracapsular extension |
| T3b | Bilateral extracapsular extension |
| T3c | Tumor invades seminal vesicle(s) |
| T4 | Tumor is fixed or invades adjacent structures other than seminal vesicles |

*PSA*, Prostate-specific antigen.

obstructive symptoms or hematuria. Bone pain is common in those patients with metastatic disease. A nodule on the prostate or induration of the gland is a hallmark sign on physical examination. It is not always specific for a carcinoma and can underestimate the extent of disease when it does represent a carcinoma.

## NATURAL HISTORY

1. Until recently the natural history of prostate cancer, especially for earlier stage disease, has been difficult to discern. Several longitudinal studies and clinical trials have provided greater information in that regard. Information regarding high-grade PIN continues to accrue and suggests that there is a progression rate from this entity to clinical cancer in a reasonable number of patients.
2. The data from the Connecticut tumor registry provide reasonable information for natural history and depict significantly worse outcomes in those individuals with higher Gleason scores.

3. Follow-up from Scandinavian, non-PSA screen-detected patient cohorts have reported a 33% rate of metastatic progression and 21% rate of prostate cancer mortality at 15 years for patients undergoing watchful waiting.
4. In patients with classic metastatic bone disease, the median survival is 27 to 33 months. Mortality is 75% at 5 years and 90% at 10 years. Recent data suggest that androgen-independent prostate cancer in the presence of metastatic disease has a median survival of 16 months.

## DIAGNOSIS AND STAGING/PSA SCREENING

1. Digital rectal examination (DRE): This is a classic component of the physical examination that, by itself, is not sensitive or specific for prostate cancer. A palpable nodule can have an approximately 50% chance of being a carcinoma. Conversely, a normal DRE does not exclude the possibility of prostate cancer.
2. Transrectal ultrasound (TRUS): Multiple studies have demonstrated that TRUS is sensitive yet not specific for the detection of prostate cancer. The classic finding is a hypoechoic lesion that in general has a 30% chance of being positive for carcinoma. Prostate cancer can also present as an isoechoic or hyperechoic lesion. The most important use of TRUS is in aiding transrectal guided needle biopsies of the prostate gland.
3. Serum markers: The classic marker for prostate cancer was acid phosphatase. The enzymatic test was elevated in 70% of patients with extracapsular and metastatic prostate cancer. The more sensitive radioimmunoassay of this enzyme is not as useful for detecting extracapsular disease and has no value as a screening test for prostate cancer. PSA is the most useful marker in the detection and monitoring of prostate cancer and is discussed in detail separately.
4. Prostate needle biopsy: Prostate biopsy is most commonly performed via a transrectal ultrasound guided approach. Contemporarily 10 to 12 cores of tissue are obtained. The procedure is generally well tolerated; however, biopsy-associated complications include hematuria, hematospermia, hematochezia, urinary retention, and, rarely, sepsis. **Postbiopsy sepsis is becoming more common with the emergence of fluoroquinolone-resistant bacteria.** The percentage of positive cores, line length, or line percentage of cancer per core can provide further predictive information with regard to staging and outcomes.

5. Bone scan: Before a lesion can be seen on a conventional radiograph, it must have replaced bone mass by 30% to 50% and be 10 to 15 mm in diameter. Plain film correlates of suspicious areas are often obtained. In some cases dedicated magnetic resonance imaging (MRI) or computed tomography (CT) imaging can resolve equivocal cases. Patients with a PSA value less than 10 ng/mL rarely demonstrate metastases.
6. CT and MRI: CT scans of the pelvis have poor performance characteristics for assessing metastatic disease and are not part of standard staging. Body coil MRI is performed similarly. Endorectal MRI may provide additional staging information in those patients with intermediate PSAs and greater than 50% positive needle-core biopsies. Additionally, data obtained by MRI spectroscopy may provide further information regarding the location and nature of malignant lesions.
7. PSA
    a. Biochemical characteristics: PSA is a 240 amino-acid single-chain glycoprotein that has a molecular weight of 34 kD. It is coded on chromosome 19 (6 Kb: 4 introns, 5 exons) and is homologous to members of the kallikrein gene superfamily and is designated human kallikrein 3 (hK3). It is a serine protease.
    b. Physiology: PSA liquefies the seminal coagulum that is formed after ejaculation. A substrate produced in the seminal vesicles has been identified. PSA has activity like chymotrypsin and trypsin. The half-life of PSA is 2.2 to 3.2 days.
    c. Marker properties: There is no PSA level that indicates zero risk of having prostate cancer. Initially a PSA value of 4.0 ng/mL was used as a cut-off point for biopsy. A value above 2.6 ng/mL in younger men has also been used as a trigger for biopsy. Serum values are not generally altered by DRE but can be affected by recumbency, urologic instrumentation, ejaculation, and prostate biopsy. Nonmalignant conditions that affect PSA levels include prostatitis, prostate infarction, and benign prostatic hypertrophy (BPH).
    d. General clinical use: The principle use of PSA is in disease detection. The most specific use for PSA is the monitoring of patients after radical prostatectomy. Postoperative baseline values should be in the undetectable range. Residual disease is suggested by any detectable postoperative levels, and values greater than 0.2 ng/mL suggest biochemical failure of therapy. It is also used to monitor the response to radiation therapy.

8. Other markers: The lack of disease specificity associated with serum PSA testing has led to investigation of more specific markers for prostate cancer. PCA3, which is a urine-based biomarker, has been shown to have increased expression in 95% of prostate cancer cases. PCA3 testing has recently been approved by the U.S. Food and Drug Administration (FDA) in the setting of an elevated PSA in men who have previously had a negative prostate needle biopsy. As discussed previously, recent discoveries in gene fusions have led to intense investigation in the utility of such markers; however, this is still considered investigation. Circulating tumor cells (CTCs) have also been investigated both in the diagnostic and therapeutic response setting. The FDA recently approved the use of CTCs in monitoring disease response in patients with metastatic prostate cancer.

## CANCER PREVENTION

1. General considerations: Because prostate cancer is relatively common, chemoprevention strategies for this disease are reasonable. However, because such therapies are delivered to large groups of cancer-free subjects, toxicity must be extremely low or nonexistent. Estimates for the number of patients requiring treatment to prevent one case of cancer demonstrate the broad range of such therapies. Given the incidence of prostate cancer in the United States, 500 men would have to be treated with an agent that could reduce cancer of the prostate by 50% to avoid one cancer. Chemoprevention strategies may therefore require additional considerations such as a focus toward higher risk populations.
2. 5-alpha-reductase inhibition: A major phase III chemoprevention trial, the Prostate Cancer Prevention Trial (PCPT), demonstrated a 24.8% reduction in period prevalence of prostate cancer in patients using 5 mg of finasteride (type II) daily compared to placebo. However, the prevalence of higher grade prostate cancer was 25% higher (6.4% versus 5.1%), dampening this overall positive result. The reasons for this increase in higher grade disease remain to be fully explained but have hindered widespread adoption of 5-alpha-reductase inhibition as chemoprevention. The REDUCE trial using dutasteride, a type I and type II 5-alpha-reductase, also demonstrated a reduction in prostate cancer detection (23% compared to placebo).

3. Toremifene: This agent is a synthetic estrogen receptor modulator (SERM) that in phase IIb/III trials demonstrated the ability to reduce the progression of those patients with high-grade PIN to prostate cancer by 22%. A more recent phase III trial including men with a history of high-grade PIN did show a 10.2% relative risk reduction for prostate cancer compared to placebo; however, it was not statistically significant.
4. Selenium and vitamin E: In large phase III chemoprevention trials targeting other primary tumors, a secondary end-point analysis demonstrated that selenium reduced the incidence of prostate cancer by 63% in a study targeting skin cancer, and vitamin E reduced prostate cancer by 32% in a lung cancer study. This provided the basis of the SELECT trial. This trial was discontinued early as it clearly demonstrated no risk reduction with either selenium or vitamin E supplementation.
5. Lycopene: This agent is a water-soluble antioxidant. There are several lines of evidence but no conclusive proof that it may have an impact on prostate cancer chemoprevention.
6. Antiinflammatory agents: General nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors demonstrate antiprostate cancer activity in the laboratory but are not under current consideration for study as chemopreventive agents because of their additional side effects.
7. Soy and other isoflavones: The components of soy may have anticancer properties, and epidemiologic studies support the potential for risk reduction by the inclusion of these substances in the diet.

## OUTCOME PROGNOSIS AND STRATIFICATION

Several statistical approaches to the stratification of patients with regard to outcomes based on clinical data have been developed. Approaches using multiple regression analysis, nomograms (Figure 16-1), and neural networks have been employed for several different scenarios for prostate cancer. Hybrids of these methods have also been tested. In general the correlation of these models to individual outcomes is in the 0.7 to 0.75 range. Nomogram strategies may provide more individualized information. All of these methods may be useful in better directing patient choices and the use of additional therapies in the future.

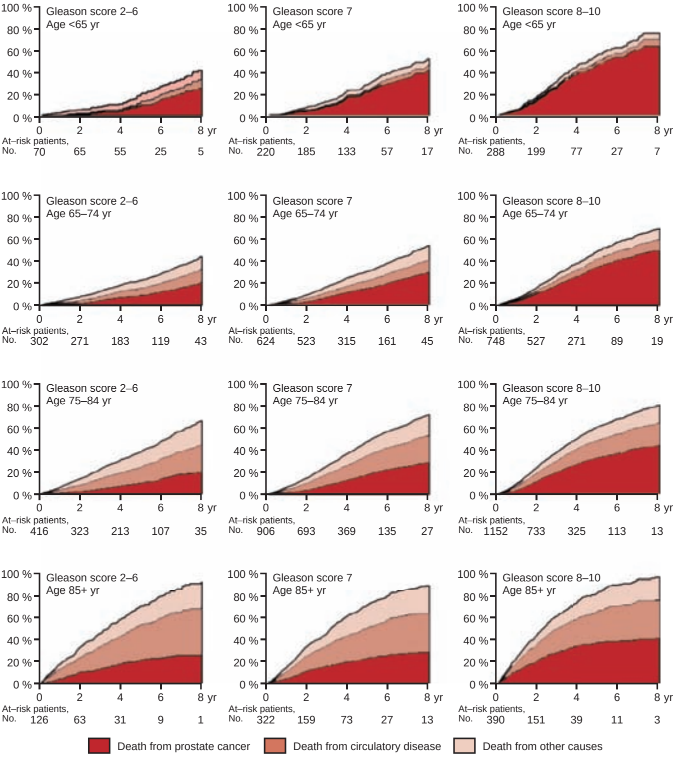

**FIGURE 16-1 Cumulative mortality from prostate cancer and other causes after diagnosis of locally advanced prostate cancer, stratified by age and Gleason score** (From Akre O, Garmo H, Adolfsson J, et al: Mortality among men with locally advanced prostate cancer managed with noncurative intent: a Nationwide study in PCBaSe Sweden, *Eur Urol,* 60:554–563, 2011.)

## TREATMENT OF LOCALIZED DISEASE

1. General considerations: In discussing treatment for prostate cancer it is important to consider patient factors such as age and general performance status as well as tumor factors such as Gleason score, initial serum PSA, and estimated clinical volumes and stage of the tumor. If a patient has less than a 50% chance for surviving 10 years due to other comorbidities, it is difficult to measure the positive effect of treatment. Patient

tolerance for the side effects of different therapies also has to be considered. It is best when patients come to a treatment decision based on consultation and input from both surgical and radiation oncology services. The stage shift in tumors due to PSA detection strategies has resulted in 5-year disease-free survival for active therapies of nearly 100%.

2. Watchful waiting: This approach has generally been reserved for men with significant comorbidities that limit their overall survival and those unwilling to consider other forms of treatment. With 15-year follow-up, the SPCG-4 trial of surgery versus watchful waiting demonstrated improved outcomes for those undergoing radical prostatectomy including metastasis rate (11.7% risk reduction), disease-specific survival (6.1% reduction), and overall survival at 10 years (6.6% reduction). These findings were more pronounced in patients younger than the age of 65 years.
3. Active surveillance: With the significant stage shift in prostate cancer, the prevalence of low-grade, low-volume cancer has increased significantly. It has been postulated that the majority of very low risk prostate cancers pose little threat to an individual's mortality. In light of this, active surveillance has become an increasingly popular option for men with low risk disease in an attempt to minimize the morbidity of treatment in those who are unlikely to die from prostate cancer. Active surveillance differs from that of watchful waiting in that there is strict surveillance by periodic DRE and PSA and repeat prostate biopsy, with the intent for curative intervention with progression to more aggressive disease characteristics. While active surveillance criteria vary from center to center, generally men considered appropriate candidates have: Gleason score less than or equal to 6 disease; less than or equal to 2 positive biopsy cores; less than or equal to 50% of any core involved with cancer; a PSA of less than or equal to 10; and a PSA density of less than or equal to 0.15. Classic triggers for intervention are volume or grade progression on subsequent biopsy. PSA doubling time has also been used by some as an indication for intervention. Approximately 30% of men in the Johns Hopkins active surveillance cohort ultimately underwent therapeutic intervention (roughly three quarters based on biopsy reclassification). With intermediate term follow-up, active surveillance has been reported to be a safe option for highly selected men with low-risk disease.

4. Radical prostatectomy: This is an appropriate treatment choice for younger patients and for older patients who are very fit and desire this form of treatment. Generally, a chronologic age of 70 is used as a relative cutoff point, but decisions need to be individualized with respect to health status and anticipated life span. Surgical mortality is less than 0.2% but 1% to 2% of patients may experience a pulmonary embolus or deep vein thrombosis. Surgical approaches include retropubic, perineal, robotic, and laparoscopic. Urinary incontinence may occur in up to 10% of patients. The potential for erectile dysfunction (ED) can be decreased with surgical approaches that spare the cavernosal nerves; however, age and preoperative erectile function are also significant predictors of ED following surgery. A bladder neck contracture can occur in 2% to 3% of patients. Disease-specific survival is in the 95% range over 10 years.
5. Radiation therapy
   a. External beam radiation therapy (EBRT): This is an option for localized prostate cancer and is the treatment of choice for T3 disease and patients unfit for surgery. Significant technical advances, such as conformal radiation and intensity modulated radiation therapy (IMRT), have allowed for the increase in dose intensity yet a decrease in overall side effects. In general, it is administered in divided doses ranging from 70 to 80 Gy and is well tolerated. Approximately 3% to 5% of patients will experience persistent rectal or bladder symptomatology; greater than 60% of patients will develop ED within 2 years. Hematuria or hemorrhagic cystitis is a late development in a small percentage of patients.
   b. Interstitial brachytherapy: Ultrasound-guided transperineal brachytherapy has become an accepted modality for the treatment of localized prostate cancer. It is difficult to treat large prostate glands (greater than 50 $cm^3$) with this technique. Intermediate term results (10 years) suggest similar outcomes to surgery or EBRT in selected patients. The usual radiation sources are $^{125}I$ and $^{103}Pd$. The principle urologic side effect is voiding dysfunction, which is usually short term but may be persistent. Those individuals with high International Prostate Symptom Score (IPSS) scores should not be considered for this technique.
6. Cryosurgical ablation of the prostate: This technique has undergone multiple modifications and is currently performed

with small-caliber needles using freeze-thaw cycles employing argon and helium gas. More recent series show less morbidity and a decrease in chronic pelvic pain noted in early reports. While cryotherapy is of controversial utility in the primary setting, it has shown value in salvage cases for local recurrence after radiation therapy.

7. High-intensity focused ultrasound (HIFU): HIFU is currently under investigation for treatment of focal and localized disease. Early data demonstrate feasibility, yet data on intermediate- and long-term outcomes and side effects are pending. HIFU is not currently FDA approved in the United States for primary treatment.
8. Posttreatment follow-up: Serum PSA is the single most important follow-up parameter in evaluating posttreatment patients with either surgery or radiation.
    a. In surgery patients, the serum PSA should drop to an undetectable level. Occasionally very low persistent PSA findings that do not progress are noted. In most cases, if the serum PSA becomes detectable and rises above 0.2 ng/mL, the patient continues to show disease progression. Biochemical failure can predate clinical failure by 6 to 8 years. Newer data suggest that biochemical failure is a surrogate marker for ultimate clinical failure and survival. However not all patients with biochemical failure will ultimately die of prostate cancer. Outcomes are heterogenic. Patients with high-grade disease who fail early and display a short doubling time may have a survival as short as 7 years, whereas patients who are late failures with lower moderate-grade disease who are progressing slowly may live as long as 19 years. Further follow-up is necessary to clearly define the true impact of biochemical failure.
    b. In general, response to radiation therapy is predicated on the pretreatment PSA and can be predicted by the posttreatment PSA. The closer to an undetectable value post treatment the better the overall outcome.
    c. There is a role for radiation therapy after postsurgical biochemical failures. Success is best when therapy is instituted before the PSA is greater than 1.0 ng/Ml, and studies have also demonstrated improved therapeutic responses at even lower PSAs. Percentage for cure ranges between 30% and 50% in different series. Salvage surgery can be employed in radiation therapy failures.

## TREATMENT OF BIOCHEMICAL AND CLINICAL FAILURE

1. In general, 25% of patients will experience a PSA recurrence in 10 years after local therapy. The exact definition of recurrence and the clinical significance of these outcomes have become somewhat clearer in the past several years. The yearly incidence of such patients in the United States is 50,000.
2. PSA failure in surgery: This definition ranges from any detectable PSA to 0.4 ng/mL. Low, stable detection of PSA may occur in postoperative patients and is often attributed to persistent benign tissue. Once the PSA value rises above 0.2 ng/mL, it rarely recedes. This value is therefore considered an absolute threshold for biochemical failure.
3. PSA failure in radiation patients: A strong definition for these patients has been more difficult to define due to the persistence of PSA detection after therapy and the kinetics involved in defining true progression from variations about a mean value. Nadir value plus two consecutive rises is the current operational definition, yet other definitions may be employed in the future.
4. Significance of biochemical failure: A rough guide to PSA failure in surgery patients suggests that there are approximately 8 years from biochemical failure to clinical failure, and 5 years from that point to cancer-related death. This could be stratified by time to failure from surgery, initial PSA and Gleason score of the tumor, and PSA doubling time. The range of values was from 7 to 19 years. Recent analysis places significant import on PSA doubling times, with a doubling time of 3 months as a surrogate marker for cancer-related death. This was noted in approximately 12% of surgery patients and 20% of radiation patients. A more recent analysis based on the stratification of time to failure (greater or less than 3 years), less or greater than Gleason score 8 cancer, and a PSA doubling time ranging from 3 to 15 months could separate out patients with a 2% to 99% chance of experiencing a prostate cancer-related death.
5. Treatment for biochemical failure
   a. Watchful waiting for late recurrence, slow velocity, long doubling-time tumors
   b. Salvage radiation therapy for surgery patients
   c. Androgen blockade for radiation patients with persistently rising PSA.

## TREATMENT OF ADVANCED DISEASE

Patients with metastatic prostate cancer are initially treated with androgen ablation therapy. This can be accomplished with gonadotropin-releasing hormone (GnRH) agonists, bilateral orchiectomy, and more recently GnRH antagonists. Diethylstilbestrol (DES) is no longer used because of increased cardiovascular risk associated with this agent. Toxicities of androgen ablation therapy include hot flashes, loss of libido, impotency, muscular atrophy, osteopenia, and osteoporosis.

Antiandrogens block the intracytoplasmic androgen receptor. Multiple trials have compared chemical castration alone to castration plus an antiandrogen (termed *total* or *maximal androgen blockade*). Meta-analysis demonstrated that total androgen blockade is associated with a very small survival advantage at 5 years. However, the antiandrogens may cause toxicity (gastrointestinal [GI], liver) and are very expensive. Patients with a rising PSA on total androgen blockade may respond to withdrawal of the antiandrogen. Ketoconazole suppresses production of adrenal steroids and may be helpful in some patients who progress despite castration.

Metastatic disease that progresses despite castration has been classically labeled as *hormone-refractory disease* (also called *androgen-independent* or *castrate metastatic*). For the last decade, cytotoxic chemotherapy in the form of docetaxel has been the standard of care in this setting. **The use of docetaxel in the metastatic, hormone-refractory setting is based on randomized trials demonstrating a modest (3-month) survival benefit.** Second- and third-generation chemotherapeutic agents, including cabazitaxel and satraplatin, have also been recently approved.

More recently, better understanding of the molecular biology of the androgen receptor has redefined the treatment of hormone-refractory prostate cancer. It has been found that the androgen receptor remains active in prostate cancer progression. Understanding of this mechanism has led to a new generation of antiandrogens including abiraterone and enzalutamide. Abiraterone is a selective steroid biosynthesis inhibitor which further decreases testosterone levels in patients who are already "castrate." Enzalutamide blocks the cytosolic translocation and DNA binding of the androgen receptor. Both of these drugs have shown promising results in the treatment of hormone refractory prostate cancer.

Immunotherapy has also emerged as a treatment option for advanced prostate cancer. Sipuleucel-T is the first cancer vaccine to gain FDA approval for metastatic, hormone-refractory prostate cancer. Phase III studies have demonstrated an approximately 4-month survival benefit in this therapy. While challenges remain on the immunotherapeutic front, including cost and a cumbersome delivery method, targeting prostate cancer with immunotherapy may hold promise in the advanced setting.

HRPC patients with bone metastases are at increased risk of skeletal complications including pathologic fracture and bone pain. A randomized trial demonstrated that administration of the bisphosphonate zoledronic acid decreases the risk of skeletal complications in men with progressive HRPC and bone metastases compared to placebo. More recently, the monoclonal antibody denosumab has been reported to reduce skeletal-related events in men on androgen-deprivation therapy. Advantages of denosumab, compared to bisphosphonates, are that it is administered subcutaneous and can also be given to patients with renal insufficiency. Important morbidity associated with bisphosphonate and denosumab therapy is osteonecrosis of the jaw (Table 16-3).

## Carcinoma of the Bladder

### GENERAL CONSIDERATIONS

Bladder cancer is the second most common urologic malignancy. The majority of cases are urothelial carcinoma, and 65% to 75% of new cases are Ta (mucosal only), T1 (lamina propria invasion), or carcinoma in situ (CIS) (flat, noninvasive). These lesions were previously grouped as “superficial” tumors, but their distinct biology warrants the stratification of these lesions. The remainder is muscle-invasive tumors. Transurethral resection (TUR) of these lesions is the principal form of diagnosis and therapy for bladder cancer. Nonmuscle invasive lesions are often further treated with intravesical therapy to reduce the risk of disease recurrence and progression. A single perioperative intravesical treatment with Mitomycin C reduces the risk of tumor recurrence. Recurrent Ta, initial T1, and CIS lesions may be treated with bacille Calmette-Guérin (BCG) intravesical immunotherapy, which can decrease tumor recurrence and reduce tumor progression. Muscle-invasive disease and treatment-resistant T1 and CIS lesions are best treated

TABLE 16-3

***The 2013 American Urological Association guidelines for PSA screening include:***

1. PSA screening in men under the age of 40 is not recommended.
2. Routine screening in men between ages 40-54 years at average risk is not recommended.
3. For men 55-69 years old, the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1000 and screened over a decade against the known potential harms associated with screening and treatment. For this reason, shared decision making is recommended for men 55-69 years old who are considering PSA screening, and proceeding based on the patient's values and preferences.
4. To reduce the harms of screening, a routine screening interval of 2 years or more may be preferred over annual screening in those men who have participated in shared decision making and decided on screening. As compared to annual screening, it is expected that screening intervals of 2 years preserve the majority of benefits and reduce overdiagnosis and false positives.
5. Routine PSA screening is not recommended in men over age 70 or any man with less than a 10-15-year life expectancy.
   - Postbiopsy sepsis is becoming more common with the emergence of fluoroquinolone-resistant bacteria.
   - Generally, men considered appropriate candidates have Gleason score ≤ 6 disease, ≤ 2 positive biopsy cores, ≤ 50% of any core involved with cancer, a PSA of ≤ 10, and a PSA density of ≤ 0.15.

with radical cystectomy and some form of urinary diversion. Combined chemotherapy and radiation approaches are useful in select patients and those who cannot tolerate surgery. Advanced disease responds to platinum and paclitaxel-based chemotherapy regimens, but sustained complete responses are rare.

## EPIDEMIOLOGY

**The United States has more than 54,000 new cases of bladder cancer yearly with approximately 10,820 cancer deaths.** Bladder cancer accounts for approximately 5% to 8% of male cancers and is the fourth most common cancer in men. It accounts for 2% of female cancers (eighth most common), and that percentage is rising. Bladder cancer is the ninth most frequent cancer worldwide with a yearly incidence of 356,000 new cases and a worldwide prevalence (5 years) of 1.1 million (U.S. estimate 500,000).

Over the past 15 years, a 40% increase in the incidence of bladder cancer has been observed in the United States.

It is three to four times more common in men, and disease risk is half as common in black Americans. Survival among women and blacks appears to be worse than in white men.

## ETIOLOGY

1. Tobacco exposure: **Tobacco use confers a two- to threefold increased risk of developing bladder cancer.** The polycyclic aromatic hydrocarbon, 4-aminobiphenyl, has been suggested as the most significant carcinogen in tobacco. Latency is approximately 20 years, and risk reduction occurs with smoking cessation.
2. Industrial exposure: The first link of industrial exposure and cancer was made between bladder cancer and aniline dyes. Textile printing and rubber manufacturing have also been established with this tumor. Major carcinogens found in such environments are 2-naphthylamine, 4-aminobiphenyl, and 4-nitrobiphenyl.
3. Age: The median age at diagnosis is 70 years. Bladder cancer is rare in persons younger than 40 years of age and tends to be less aggressive in younger age groups.
4. Chemotherapy: Cyclophosphamide and ifosfamide have been associated with the development of bladder cancer. The presence or absence of hemorrhagic cystitis is not associated with the likelihood of developing cancer. The use of reducing agents (mesna), hydration, and catheter drainage during therapy have probably decreased the development of cancer with these agents.
5. *Schistosoma haematobium:* Infection is common in many areas of North Africa, and the deposition of ova in the bladder lead to inflammation and the development of carcinoma. Inflammation in the presence of nitrites from bacterial activity is also implicated. Additionally, heavy tobacco use and exposure to nitrate-containing fertilizers are endemic in these areas. The majority of these tumors are squamous carcinoma.
6. Chronic irritation and infection: Chronic infection carries a slightly increased risk of developing bladder cancer, and those patients with a chronic indwelling Foley catheter have a 10- to 20-fold increase in developing bladder cancer (primarily

squamous). Premalignant changes can be noted after a few years, and yearly cystoscopic evaluations are recommended.

7. Genetic predisposition: Differences in metabolism of toxins rather than germline mutations play a role. N acetyltransferase 2 (slow acetylators), glutathione S-transferase M1 homozygous deletions, and CYP2A1 expression all add to risk.
8. Pelvic irradiation: This is associated with an approximate 10% increased risk of developing bladder cancer. Newer methods of conformal radiation may lessen the risk to nontarget organs.
9. Additional risks: Arsenic in the water supply, the ingestion of the Chinese herb *Aristolochia fangchi*, and ingestion of ochratoxin A (in bracken fern) may also contribute to the development of bladder tumors. Ingestion of phenacetin is associated with the development of upper urinary tract transitional cell carcinoma (TCC).

## PATHOLOGY

1. Normal urothelium demonstrates basal, intermediate, and superficial cells. There are usually seven cell layers.
2. Hyperplasia is generally described as thickened mucosa without cellular atypia.
3. Urothelial dysplasia: Preneoplastic changes in the basal and intermediate layers with the presence of cell cohesion, yet some architectural disruption; progresses to frank neoplasia in 15% to 20% of cases.
4. CIS: This is a cytologically malignant flat lesion with prominent disorganization of cells, loss of cell cohesion, loss of cellular polarity, and coarse chromatin. Pagetoid, small cell, and large cell variants have been described. CIS is a noninvasive lesion, but if it is left untreated, 20%-83% of patients will progress to invasive carcinoma.
5. Urothelial papilloma: This is a benign exophytic neoplasia with normal-appearing urothelium on a fibrovascular core. It usually appears as solitary lesions. An inverted papilloma growth variant also exists.
6. Papillary urothelial neoplasm of low malignant potential (PUNLMP): This is similar to papilloma but with increased cellularity; it is associated with greater propensity for recurrence progression and rare mortality.

7. Papillary urothelial neoplasm low grade: Papillary morphology with variable architecture and mitoses at all levels; altered CK20 expression FGFR3 mutations in 80% of cases.
8. Papillary urothelial neoplasm high grade: Marked architectural disorder with papillary fusion and variable cell number thickness; demonstrates significantly more molecular alterations.
9. Stromal invasion (T1): Tumor invades the lamina propria but not the muscularis propria. Attempts at subdivision have been made with regard to depth of lesion, vascular invasion, and muscularis mucosa involvement.
10. Invasive urothelial carcinoma: Tumor invasion into true muscularis propria; almost exclusively high grade; tumor front may be "pushing" or tentacular.
11. Squamous carcinoma: This uncommon cancer (3% to 7%) is distinct from squamous metaplasia. It is associated with chronic irritation or schistosomiasis and has a greater tendency for local recurrence when treated.
12. Adenocarcinoma: This is a rare tumor (1% to 2%) associated with urachal carcinoma at the bladder dome. It is necessary to rule out GI tract or breast metastases before designating it as a primary tumor.
13. Small cell carcinoma: The has a neuroendocrine origin. It is highly aggressive with presentation at high pathologic stage and responds poorly to any therapy.
14. Micropapillary carcinoma: This is an aggressive variant of bladder cancer that resembles papillary serous carcinoma of the ovary. Noninvasive and invasive presentations have been reported.

## GRADING AND STAGING SYSTEM

1. The World Health Organization (WHO) 2004 grading system is the most widely accepted grading system. It categorizes tumors into low or high grade, allowing for ease of interpretation.
2. Staging is best achieved with the TNM classification, which subdivides the different levels of muscle invasion and extravesical extension. **Stage and grade are both significant predictors of recurrence and progression.**

## NATURAL HISTORY

The natural history of bladder tumors with regard to recurrence and progression is closely related to the stage and grade of the lesion. The distinct classifications of noninvasive tumors as opposed to lumping them as superficial lesions demonstrate these differences.

1. Low-grade Ta lesions
   a. Noninvasive low-grade lesions account for 25% to 50% of bladder tumors. Those lesions defined as PUNLMP demonstrate a recurrence rate of 30% to 50%, but with 5- to 10-year follow-up, no episodes of progression are noted. In low-grade lesions, tumor multiplicity, recurrence at 3-month cystoscopy, and tumor size greater than 3 cm are factors favoring recurrence.
   b. Low-grade Ta lesions carry a 30% to 60% risk of recurrence and a 0.2% to 5% risk of progression after five years.
2. High-grade Ta lesions
   a. These lesions account for 3% to 18% of most series with an average incidence of 6%. This is a difficult tumor to distinguish pathologically, and on comparative review many of these lesions (up to three fourths) are restaged as T1 lesions.
   b. These lesions demonstrate a 20% to 25% risk of tumor stage progression.
3. CIS
   a. These lesions account for 5% to 10% of all superficial bladder cancer, and by definition are high-grade tumors.
   b. A suggestion of clinical subtypes has been made: primary disease, secondary CIS (detected after prior papillary disease), and concurrent CIS (CIS in the presence of papillary tumors). Primary disease accounts for 30% of cases, secondary 42%, and concurrent 28%. The distinction of primary asymptomatic unifocal CIS and symptomatic multifocal primary CIS has also been advanced.
   c. **Overall, 54% of patients with CIS progress to muscle-invasive disease.** Concurrent CIS has the highest progression rate to T1 disease (60%) and primary CIS the lowest (8% to 28%).
   d. Asymptomatic patients account for 25% of patients, whereas 40% to 75% of patients will have irritative bladder symptoms.

4. T1 bladder tumors
    a. T1 lesions comprise 25% to 30% of superficial bladder tumors. **They will recur in up to 80% of cases and demonstrate tumor progression in 20% to 50% of cases.** Those with deep invasion to the layer of the muscularis mucosa have a more aggressive history with a progression rate of 40% and 5-year survival of 50%.
    b. Rebiopsy of T1 lesions can result in upstaging of the initial lesion in 30% to 60% of cases. This is especially true when no muscle is noted on the initial biopsy. Persistent tumor on repeat biopsy can also be a poor prognostic indicator for response to therapy.
5. Muscle-invasive disease

    Patients with muscle-invasive disease demonstrate stage progression and tumor metastases to lymph nodes, lung, liver, and bone. The majority of untreated patients (80% to 90%) will demonstrate a cancer-related death in 2 to 3 years.

## SIGNS AND SYMPTOMS

1. The most common symptom of bladder cancer is microscopic or gross hematuria followed by irritative bladder symptoms. Bladder masses can also be found as incidental findings on imaging examinations or as incidental findings during a cystoscopic examination.
2. **Hematuria in some form is noted in 85% of cases of bladder cancer.** Bladder masses on imaging can represent stones or polypoid cystitis. Additionally, the absence of a mass on imaging does not rule out the presence of a bladder tumor, which may not be detected because of tumor size or incomplete filling of the bladder.

## DIAGNOSIS OF BLADDER CANCER

1. The evaluation of a suspected bladder mass should consist of an imaging exam, visual inspection of the urothelium, and cytologic evaluation of the urine. The role of additional urine-based tumor markers, both for the diagnosis and surveillance of bladder cancer, continues to evolve.
2. The classic imaging modality for the urinary tract has been the intravenous urogram (pyelogram). With improvements in technology, the CT urogram and MR urogram have become very popular. Ultrasound resolution is too low to

discern small upper tract lesions or many bladder lesions and does not evaluate the ureters. In the case of renal insufficiency, an ultrasound can evaluate the renal parenchyma, and the urinary tract can be evaluated with retrograde pyelograms and cystoscopy.

3. Urinary cytology: This cellular evaluation has poor overall sensitivity but is very specific for high-grade disease and CIS. Although the performance characteristics are rather poor for low-grade, low-stage lesions, high-grade tumors, and CIS, which may not be easily seen on cystoscopy, can be detected with a sensitivity in the 80% range and a specificity of 90% to 95%.
4. Cystoscopy: Endoscopic evaluation of the urothelium can be carried out by rigid or flexible optical scopes that allow one to examine the urethra, prostatic fossa, and bladder lining. It is the "gold standard" for the evaluation of the urinary tract lining; however, it is not 100% accurate. Small tumors and areas of CIS may be missed on exam. Enhanced imaging with fluorescent imaging may improve detection and is currently being evaluated.

## DISEASE SCREENING AND TUMOR MARKERS

1. Hematuria screening: No prospective studies demonstrate a decrease in bladder cancer-related deaths as a function of screening. Comparisons of screened and unscreened populations suggest a shift in the detection from T2 to high-grade noninvasive disease with serial dipstick hematuria screening. This suggests that high-risk populations such as male smokers or those with high-risk occupational exposures and older than 50 years may benefit from this activity.
2. Tumor markers: Several protein-based and genomic-based markers have been evaluated for their role in the detection and surveillance of bladder cancer. A few have FDA approval for the monitoring of bladder cancer. In general, the protein markers have high sensitivity but lack specificity as tumor markers. They are more sensitive than urine cytology for the detection of lower-grade tumors and often less sensitive than cytology for high-grade disease or CIS. The performance of the protein-based markers can be degraded by inflammation and hematuria. False-positive tests create test anxiety but in some cases may detect disease before it is clinically evident. False-negative tests result in missed diagnosis

and tumor progression. In general, these markers have the potential to make detection and monitoring of bladder cancer more precise, but no marker has been definitively established in this role.

a. Protein-based markers
    1) NMP22: This is a nuclear mitotic protein that is released in urine. It has been available as a laboratory test and now a point-of-contact test. A general cutoff value has been 10 U/mL, but different values have been used. The specificity ranges between 60% and 80%, and the sensitivity ranges between 18% and 100%. It is approved as an aid in the diagnosis of patients at risk for bladder cancer and for disease monitoring.
    2) BTA: This test detects a complement factor H-related protein and complement factor H. It exists as a point-of-contact test and a standard enzyme-linked immunosorbent assay (ELISA). Sensitivity ranges from 10% to 90%, and sensitivity is near 90% in healthy patients. This, however, is degraded by inflammation and hematuria to the 50% range. It is not useful for the detection of disease and is approved as an aid in managing bladder cancer.
    3) Hyaluronic acid-hyaluronidase (HA-HAase): This test measures HA and HAase ELISA assays. It has an 83% sensitivity and 90% specificity in detecting bladder cancer. It appears to be less affected by inflammation or hematuria, and false-positive studies have a 10-fold risk of tumor recurrence within 5 months. It has yet to undergo multicenter trials.
    4) ImmunoCyt: An immunocytologic evaluation of exfoliated cells with three antibodies. This test in conjunction with cytology has a combined sensitivity of 90% and specificity of 79%. This falls off, however, in patients with hematuria, cystitis, or BPH.

b. Genomic-based markers
    1) UroVysion test, fluorescent in situ hybridization (FISH): This is a multitarget FISH assay that evaluates alterations in ploidy with three chromosome enumeration probes 3, 7, and 17 and one locus-specific identifier 9p21 (p16 locus). Sensitivity is between 60% and 100% for low- to high-grade tumors, and specificity is approximately 95%. It is approved for the detection and monitoring of bladder cancer.

2) Microsatellite analysis: This assay evaluates loss of heterozygosity at several loci in the genome. Sensitivity ranges between 72% and 97%. Specificity is high in healthy populations but may be altered in cystitis and BPH. No standardized set of markers is in use and prospective studies are in progress.

## CLINICAL STAGING AND IMAGING

1. TUR: TUR by the method of electrocautery is the classic method for initial treatment and staging of bladder tumors. A blended current of cutting and cautery is employed, and an effort to resect the entire tumor with deep muscle biopsy is made. The potential for bladder perforation exists and generally may be treated by prolonged catheterization when extraperitoneal. Intraperitoneal perforation may require an open repair. Patients can demonstrate hematuria and irritative symptoms for several weeks after the procedure.
2. Random biopsies: The routine use of random biopsies has not been established, yet they can be useful in determining the extent of disease such as CIS and the presence of disease in sites such as the prostatic urethra. They have a greater role in higher grade and stage noninvasive lesions. It is less common to detect disease from normal-appearing areas of the bladder when low-grade Ta lesions are present.
3. Fluorescence cystoscopy: Compared to standard white-light cystoscopy, this method requires the use of a blue light and the photosensitizer hexaminolevulinate. This approach potentially allows for better visualization of CIS and small tumors which can be missed with white-light cystoscopy. Some studies have shown a decrease in tumor recurrence using this technique. Fluorescence cystoscopy may also be useful in patients with a persistently positive cytology and a negative white-light cystoscopy.
4. CT scanning and MRI scanning do not provide precise information regarding clinical stage (invasive). Sensitivity is in the 70% to 90% range with specificity in the similar range. Accuracy is in the 55% to 85% range. Operational characteristics for defining lymph node status is somewhat higher. These modalities are also useful for demonstrating the absence or presence of hydronephrosis.

5. Bimanual examination under anesthesia: This maneuver is still valuable in assessing the status of patients with muscle-invasive tumors and provides information with regard to tumor extent and pelvic or abdominal wall involvement.

## THERAPY IN GENERAL

1. TUR
   Surgical excision alone may be adequate in the treatment of low-grade Ta disease. Fulguration about the perimeter of resection and care in avoiding gross perforation enhance the effectiveness of this technique.
2. Laser ablation of bladder tumors
   This is an effective method of treating bladder lesions, but a major drawback is the lack of pathologic specimen. It has advantages for patients on anticoagulation therapy and causes less pain and no obturator reflex. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is popular for this purpose.
3. Intravesical chemotherapy instillation
   a. General considerations: Cytotoxic chemotherapy agents have been administered within the bladder with the objective of eradicating existing tumors, preventing the recurrence of treated tumors, and possibly preventing or delaying tumor progression. The ideal agent would be nontoxic, effective in a single dose, and inexpensive. No such ideal agent exists, but several agents demonstrate activity against noninvasive lesions.
   b. The summary analysis of multiple studies looking at the efficacy of chemotherapy demonstrates that in the short term these agents reduce recurrence by 14% to 17%. Over 3 to 5 years, this effect is reduced to approximately 7%. Several large series of intravesical chemotherapy with a median survival follow-up of nearly 8 years demonstrate that there is no advantage to inhibiting tumor progression with this form of therapy. Most of these data are compiled from six-course administrations. Data evaluating combined or sequential chemotherapy generally demonstrate no therapeutic advantage but an increase in side effects. Some work on sequential mitomycin and gemcitabine suggests some potential synergy. Combined chemotherapy and immunotherapy have likewise shown additive value.

   c. Immediate instillation of single-dose therapy. **The meta-analysis of seven clinical trials demonstrates that immediate instillation of a single dose of intravesical chemotherapy can decrease Ta and T1 tumor recurrence by approximately 39%.** This was most effective in patients with a single tumor, but it had some effect on patients with multiple lesions. The principal impact on recurrence occurred over the first 2 years. The mechanism is probably through an inhibition of tumor reimplantation after TUR. This form of therapy is contraindicated if a bladder perforation is noted during tumor resection. BCG cannot be used in this approach because of the possibility of intravascular inoculation and possible sepsis.

4. Optimization of therapy
   Attempts to optimize therapy include dehydration prior to instillation, alkalinization of urine, administration of small volumes of intravesical fluid, and maximum dwell times. Studies with mitomycin C suggest that this can improve time to recurrence and recurrence-free survival. Additionally, research is progressing with drug delivery enhanced by electromotive administration and thermotherapy.
5. Common intravesical chemotherapy agents
   a. Mitomycin C: An alkylating agent that inhibits DNA synthesis by cross-linking, mitomycin C is cell cycle nonspecific. The molecular weight is 334 kD; therefore there is negligible systemic absorption. The most frequent side effects are chemical cystitis in up to 40% of patients and palmar rash or other cutaneous symptoms in up to 10% of patients. It is usually administered as 40 mg in 40 mL of solution.
   b. Doxorubicin: This is an anthracycline antibiotic that binds DNA base pairs and inhibits topoisomerase II and protein synthesis. It has a high molecular weight of 580 kD, and 25% to 50% of patients can develop chemical cystitis. The usual dose is 50 mg in 30 mL of solution with ranges reported from 30 to 100 mg.
   c. Thiotepa: One of the first intravesical agents, thiotepa is an alkylating agent and is not cell cycle specific. At a molecular weight of 189 kD, it can be absorbed systemically causing thrombocytopenia in 3% to 13% of patients and leukopenia in 55% of patients. The usual dose is 30 mg in 15 mL of sterile water.

d. Valrubicin: This is a lipophilic, semisynthetic analogue of doxorubicin that demonstrates a 21% response in BCG refractory patients.
e. Newer agents, such as gemcitabine and taxanes: Gemcitabine is a novel deoxycytidine analogue (2',2'-difluoro-2' deoxycytidine) that has shown single agent activity in advanced bladder cancer. The molecular weight is 299.7 kD. Dose range has been 1000 to 2000 mg. Grade 1 hematologic complications have been noted in 5% to 15% of patients. In phase II testing, response rates have been greater than 50% in pretreated tumor populations. Studies for both gemcitabine and taxanes have shown mixed results, typically in heavily pretreated populations.

6. BCG therapy

BCG is an attenuated strain of *Mycobacterium bovis* developed in 1921 and used as a tuberculosis vaccine. In 1976, BCG's efficacy against nonmuscle invasive bladder cancer was demonstrated by Dr. Alvaro Morales. **Collective series demonstrate a 60% to 80% response rate against CIS, a 45% to 60% chance of eradicating residual papillary disease, and a 40% improvement over TUR alone for disease prophylaxis.**

The exact mechanism of BCG action is incompletely understood. Direct cell contact is necessary, and it appears that a TH1 immune pathway is predominant. Some activation of TH2 pathways are also seen, as is nitric oxide synthetase (NOS) activity. Recruitment of polymorphonucleocytes to the area of inflammation may provide further cytotoxic agents for tumor cell killing.

No data demonstrate the optimal schedule for BCG therapy. The most commonly accepted program has been designated the *6+3* program consisting of 6-week induction therapy followed by three booster treatments at 3- to 6-month intervals anywhere from 2 to 3 years. Irritative side effects can be significant and limit the long-term application of this strategy.

BCG appears to be the only intravesical agent that can decrease tumor progression. This has been demonstrated in meta-analysis and is powered by those clinical series in which maintenance BCG in some form was administered. The persistence of this effect over the long term (10 to 15 years) is questionable. The effect of BCG on overall patient survival so far demonstrates no advantage.

BCG produces irritative bladder symptoms in 90% of patients. Other symptoms include hematuria, low-grade fever, malaise, and nausea. Treatment with isoniazid and fluoroquinolones may be required. Patients with high fever (greater than 103°F or 39.4°C) require hospitalization and treatment with isoniazid 300 mg and rifampin 600 mg. A fluoroquinolone may also be used. BCG sepsis is rare, occurring in early series in 0.4% of patients. Patients with sepsis are treated with isoniazid, rifampin, and ethambutol 1200 mg daily plus a fluoroquinolone. Steroid therapy may be added. Additionally, one should consider and cover for gram-negative sepsis. Severe side effects may be reduced when direct intravascular absorption can be avoided such as traumatic catheterization, administration of BCG in the presence of an active urinary tract infection (UTI), or administration early after TUR.

Anatomically protected sites include the prostatic urethra and the distal ureters. Limited series suggest that a TUR of the bladder neck and prostatic fossa can provide better access for BCG, allowing a response in 50% to 80% of patients with superficial or ductal involvement.

## TREATMENT OF LOW-GRADE TA DISEASE

1. The contemporary data suggest that such patients should be treated with a single perioperative intravesical instillation of a chemotherapeutic agent as described previously, unless there is evidence of a bladder perforation.
2. If the tumor is visually completely resected, immediate reresection is not warranted.
3. Little evidence supports the use of BCG in these patients. Patients with recurrent disease, especially multiple recurrences and/or associated CIS, may benefit from BCG therapy.
4. Small low-grade recurrences may be treated by office fulguration.
5. Cystoscopy disease status at 3 months and tumor size greater than 3 cm predict recurrence and possible progression.

## TREATMENT OF HIGH-GRADE TA DISEASE AND CIS

1. Evidence-based data are sparse for the treatment of high-grade Ta lesions because of the small percentage of overall tumors.

2. Immediate intravesical instillation is warranted with second-look cystoscopy and TURBT with possible bladder mapping and BCG therapy with maintenance for persistent or recurrent high-grade Ta disease.
3. Consider cystectomy for original high-grade Ta if there is progression to T1 disease or CIS after BCG.
4. Maintain long-term, close (6-month) follow-up.
5. BCG demonstrates a 72% to 90% complete response in patients with only CIS. Initial response does not predict durability because up to 50% of patients may recur or progress.
6. Intravesical chemotherapy demonstrates a 35% to 53% response rate with wide variance about that interval given the studies evaluated.
7. TUR alone demonstrates a 0% durable response at 3 years.
8. In trials comparing BCG to chemotherapy, 68% of BCG and 49% of chemotherapy patients demonstrate a complete response. The BCG response is durable in 68% of patients compared to 47% of chemotherapy patients. Overall, disease-free rates at nearly 4 years are 51% for BCG and 27% for chemotherapy.
9. Maintenance therapy with BCG results in an improvement in complete response from 55% to 84%. Maintenance consists of a 3-week course of therapy every 6 months for 2 to 3 years. Patients may experience complications of bladder dysfunction. Decreased dose therapy (⅓, 1⁄10, 1⁄30, 1⁄100 of normal dose) may allow completion of therapy.
10. Disease progression in CIS is reduced by at least 35% with BCG. This effect is more prominent early. Long-term effects are less clear.
11. Treatment of BCG failures includes further therapy with valrubicin, additional therapy with intravesical interferon and BCG, or cystectomy. Valrubicin responses are in the 20% range. Forty percent to 50% of BCG failures may respond to combined BCG and interferon. Photodynamic therapy is an historical option.

## TREATMENT OF T1 DISEASE

1. Repeat TURBT for staging is mandatory. Intravesical immediate instillation of chemotherapy should be performed even with suspected T1 lesions.

2. Immediate cystectomy versus BCG
   a. Argument for cystectomy is 30% upstaging in multiple series. Chemotherapy is associated with 33% progression and is not a good option unless patient cannot tolerate a cystectomy.
   b. BCG treated T1 disease associated with an average of only 12% recurrence (0% to 35%). Overall treatment failure, including any recurrence, is 40% to 50%.
   c. Immediate cystectomy carries the morbidity and mortality of cystectomy. Surgery does not provide 100% 5-year survival (85% to 90%).
   d. Some stratification of high-grade T1 may be useful. Those with accessible, unifocal tumors, no CIS, and less than T1 disease on reTURBT may benefit from initial therapy. Those with multifocal disease, concomitant CIS, residual T1 on reTURBT, and tumors in difficult locations may benefit from cystectomy.
3. BCG therapy
   a. BCG failure may require stratification.
      1) Refractory disease: Worsening or nonimproved disease at 3 months or persistent disease at 6 months
      2) Resistant disease: Recurrent or persistent at 3 months but of lesser intensity; cleared at 6 months
      3) Relapsing: Recurrent after disease-free status achieved at 6 months
      4) Intolerant: Persistent or recurrent disease after less than adequate treatment because of patient tolerance
   b. Overall a second course of BCG may be useful in high-grade T1 patients, but therapy should not persist beyond two courses due to a significant risk of progression.

## CYSTOSCOPIC SCHEDULE AND UPPER URINARY TRACT FOLLOW-UP

1. Cystoscopic schedules have been developed on the basis of authority opinion. Usually patients undergo cystoscopy every 3 months for the first 1 to 2 years, every 6 months for the next year, and either yearly exams thereafter or an exam every 6 months for 5 years in high-risk patients. A recurrence calls for a return to evaluations every 3 months.

2. Data on low-grade Ta disease suggest that evaluations can be of lesser intensity. Although irritating, patients are willing to forego regular cystoscopy on the basis of the results of a tumor marker only if that marker would be 95% accurate. Cystoscopy findings at 3 months also influence patterns of recurrences.
3. Upper tract disease is uncommon in low-grade Ta disease yet can occur in more than 20% of patients with high-grade disease or CIS. Actuarial recurrence of upper tract disease has been reported as high as 40% over 15 years in high-risk patients. Upper tract imaging yearly or every other year is indicated for the intermediate time frame for such patients.

## TREATMENT OF T2 AND GREATER DISEASE

1. Radical cystectomy

   This is the standard of care in treating muscle-invasive bladder cancer. A radical cystectomy entails en bloc removal of the bladder, prostate, seminal vesicles, and proximal urethra. If the prostatic urethra is involved with tumor, a total urethrectomy is also carried out. This can also be performed as a subsequent separate procedure. An intact urethra is monitored by routine urethral cytology and/or urethroscopy in the postoperative period.

   In females, an anterior exenteration is performed that includes removal of the bladder, entire urethra, and anterior vaginal wall, a total abdominal hysterectomy and bilateral salpingo-oophorectomy. An en bloc pelvic lymph node dissection starting at the aortic bifurcation or common iliac vessels is performed in both sexes. The risk of recurrence for patients with radical cystectomy alone is shown in Figure 16-2.

   Urinary diversion is an integral component of the procedure and accounts for most of the long-term postoperative morbidity. The major forms of diversion include a standard ileal conduit, colon conduit, or continent urinary diversion, which may be cutaneous or orthotopic. Operative mortality for radical cystectomy and urinary diversion is roughly 1% to 3%. Early and late postoperative complications range from 10% to 50%.
2. Partial cystectomy

   This technique may be employed on a very selective basis for circumscribed lesions usually in the dome of the bladder where a 1- to 2-cm free margin may be obtained without requiring a further procedure such as ureteral reimplantation.

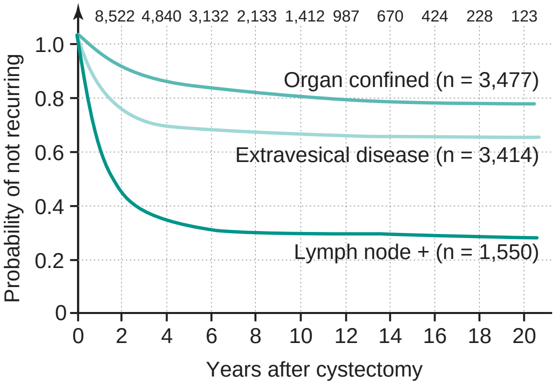

**FIGURE 16-2 Kaplan-Meier (KM) curve** (From Bochner BH, et al: Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol* 24:3967–3972, 2006.)

This procedure can be overextended in the hope of preserving a normal lower urinary tract. This should not be the case in the present era of continent urinary diversion.

3. Radiation therapy

Definitive radiation therapy has been employed in invasive bladder cancer. Overall, durable complete responses are 40% and are much poorer stage-for-stage than those obtained with surgery. Interstitial radiation therapy (iridium needles) has been employed primarily in Europe. Careful patient selection is necessary to obtain success.

4. TUR

In the case of patients who are severely medically compromised, radical TUR may be an appropriate form of therapy for invasive lesions. In addition, laser irradiation may be employed in this situation. A complete response may be obtained in as many as 20% to 30% of patients. Reports of greater success also incorporate salvage cystectomy as part of the therapy.

5. Combined modality therapy

TUR, platinum-based combination chemotherapy, and EBRT has gained increased popularity over the past several years. Studies have demonstrated survival rates equivalent to that of cystectomy in highly selected populations. Patients ideally suited for this approach typically classically have unifocal tumors, no CIS, a complete TUR, and no hydronephrosis.

Long-term follow-up is necessary to gauge duration of response and side effects on lower urinary tract function.

## URINARY DIVERSION

1. General considerations

   Urinary diversion is an integral part of urinary reconstruction and urologic oncology. Such surgery can be technically advanced and is associated with potential long-term and short-term complications. Additionally, careful consideration must be given to the physiologic costs of diverting the urinary tract and the appropriate selection of patients for a particular procedure. Urinary diversion can consist of simple diversion of the ureters to the skin, diversion of urine into the alimentary tract, or diversion of urine into an isolated segment of bowel serving as a conduit or reservoir for urine. There is no one preferred method of performing urinary diversion; therefore fundamental principles of reconstruction must be understood to appropriately apply these techniques in a given situation.
2. Forms of urinary diversion (noncontinent)
   a. Ileal conduit

      Since its introduction in 1950, the ileal conduit has become the reference standard for urinary diversion. Approximately 15 to 20 cm of terminal ileum is isolated from bowel continuity, allowing this bowel segment to serve as a conduit or passageway to the skin. General complications are listed in the following.
      1) Cutaneous considerations: The loop may be matured at the skin as a Brooke ostomy or as a Turnbull loop. The latter is useful in patients with a thick abdominal wall. One of the several ostomy appliances is attached to this site. Appropriate preoperative marking on the abdominal wall and care in constructing the stoma bud are important to avoid difficulties with patient comfort and skin care. Stomal stenosis is the most common long-term complication of cutaneous urinary diversion.
      2) Ureteral considerations: The ureteral/enteral anastomosis is a potential site for complications. A direct anastomosis between the bowel and ureter with mucosa-to-mucosa apposition is the preferred method of construction. Early ureteral leakage was a significant and morbid complication of this procedure that has been reduced by greater attention

2. History

   During the mid and late 19th century many efforts were made to divert urine into the alimentary tract in an attempt to treat congenital malformations such as bladder extrophy or conditions such as bladder cancer. Multiple complications occurred due to technical limitations in the preantibiotic era. The ureterosigmoidostomy of Robert Coffey provided one of the first reasonable methods of diverting the urinary system. Metabolic complications and the development of adenocarcinoma at the ureter-bowel junction discouraged further widespread use of this technique. The ileal loop urinary conduit described by Eugene Bricker in 1950 became the standard form of urinary diversion over the next several decades. Different techniques of continent urinary diversion have since been developed and modified by multiple individuals. The application of continent diversion has been further aided by the acceptance of clean intermittent catheterization as an appropriate form of urinary drainage.

3. General physiologic considerations

   a. Renal function

   Approximately 30% of patients will experience long-term (5 to 15 years) renal deterioration after urinary diversion. It must be remembered, however, that not all renal units associated with a diversion are normal preoperatively. This deterioration can be hastened by high static pressures within the reconstructed urinary tract, reflux, or chronic infection. Many of the metabolic abnormalities described below first became manifest or are exacerbated by patients displaying a serum creatinine greater than 2 ng/dL. Care must therefore be taken when considering such patients for urinary diversion.

   b. Infection

   The majority of patients with a urinary diversion will display urine colonized with bacteria. In general there is no concomitant symptomatic infection, and this situation is best left untreated. Repeated therapy for asymptomatic colonization can lead to infection with stone formation or severely resistant strains of bacteria. This may necessitate the use of parenteral antibiotics. Classically 4% to 6% of patients with urinary diversions may eventually die of urosepsis.

   c. Urolithiasis

      This may occur in 2% to 10% of patients with urinary diversions. The presence of foreign bodies, especially staples, provides a nidus for stone formation. Stones also have a greater tendency to form in patients with *Proteus* UTIs and in patients with hyperchloremic metabolic acidosis.

4. Metabolic considerations
   a. Electrolyte abnormalities

      These occur secondary to the interaction of urine with a particular bowel epithelium. The altered transport of different ions gives rise to particular metabolic abnormalities.

      1) Colon: The classic abnormality seen in ureterosigmoidostomy is hyperchloremic metabolic acidosis. It was first recognized by Ferris and Odel in 1950. The condition can be seen in as many as 80% of patients and is exacerbated by the large surface area of the colon exposed to urine. Essentially, a significant amount of bicarbonate equivalents is lost into the colonic urine with the absorption of chloride from the urine. This condition can lead to a severe acidosis that is exacerbated by compromised baseline renal function. Another less recognized complication can be total body potassium depletion and hypokalemia. Furthermore, elevated ammonia levels may develop in patients secondary to bacterial overgrowth. This is best treated by adequate urinary drainage and/or treatment with neomycin or lactulose.
      2) Ileum: Hyperchloremic metabolic acidosis is also seen in patients with ileal conduits. Although the findings are less severe, they can be present in as many as 70% of patients with ileal conduits. Again, patients with impaired baseline renal function will display a greater propensity toward metabolic derangement.
         a) Monitoring: McDougal and Koch emphasize the potential implications of long-term subtle metabolic abnormalities such as growth retardation and osteomalacia. The exact timing for intervention in subtle acidosis is not clear, especially in elderly adults treated for cancer, yet these issues are of great concern in the pediatric and young adult population.

b) Treatment: Hyperchloremic acidosis is treated by alkalizing agents such as oral sodium bicarbonate, Polycitra, or Shohl solution. If a sodium cannot be tolerated, cyclic adenosine monophosphate (cAMP) inhibitors such as nicotinic acid and chlorpromazine may be employed. Although sodium overload is avoided with such therapies, potential side effects such as peptic ulcer disease and tardive dyskinesia can occur.

3) Jejunum: Use of this bowel segment is associated with a hyponatremic, hypochloremic, hyperkalemic, metabolic acidosis. This is due to a loss of salt and an increase in potassium and hydrogen ions. A feed-forward mechanism is established by the initial loss of salt and water, followed by a renin-aldosterone response to the hypovolemia. The permeable jejunal epithelium is presented with a low-sodium, high-potassium urine, which facilitates further body loss of sodium into the conduit and reabsorption of potassium. Initial management requires fluid resuscitation followed by long-term sodium chloride supplementation.

4) Stomach: This bowel segment has been employed in urinary diversion or bladder augmentation in several different configurations. It has been employed predominantly in the pediatric population. The advantages of using stomach include compensation for preexisting metabolic acidosis, conversation of GI absorptive area, and decreased mucus production. The most common metabolic side effect is a hypokalemic, hypochloremic, metabolic alkalosis such as that seen with prolonged nasogastric suction. It is best managed with good oral fluid intake.

5. Other considerations

a. Neoplasia

Reports of adenocarcinoma in patients with ureterosigmoidostomies were first made in 1929. This event will occur in approximately 10% of such patients with a latency period of 10 to 20 years. Because serial screening was not performed, original reports displayed generally advanced disease with up to a 36% mortality rate. Although the lesion is usually at the ureter-colon junction, it is difficult to discern the issue of origin. The etiology of these carcinomas is poorly understood. Cases of carcinoma have been reported in ileal conduits and cystoplasties. The long-term implications for continent diversion are unknown.

b. Drug absorption

A large bowel segment provides a significant reabsorptive area for many chemicals. This is important because many patients undergoing chemotherapy for bladder cancer may be at risk for intoxication. Methotrexate, which is used with vinblastine, adriamycin, and cisplatin in the MVAC regimen, has been reported to cause toxicity. Anticonvulsant agents may also be reabsorbed by the bowel of a urinary diversion.

c. Vitamin $B_{12}$ metabolism

Vitamin $B_{12}$ is absorbed primarily in the terminal ileum, which is often isolated from the alimentary tract when constructing a continent reservoir. Because usual body reserves are adequate for approximately 5 years, this is not an immediate postoperative concern, but it must be addressed with regard to replacement therapy in patients over the long term. The 15- to 20-cm segment employed in a standard ileal conduit usually does not deplete the absorptive distal ileum still in continuity with the alimentary tract.

d. Hematuria-dysuria syndrome

This is a complex of symptoms in patients with a diversion or bladder augment from a gastric segment, which includes bladder spasm, urethral pain, gross hematuria, and skin irritation. The etiology is incompletely understood yet is probably related to the secretion of gastric acid. The activation of pepsinogen to pepsin at a low pH has been proposed as the urothelial irritant. It is best treated by oral hydration and histamine blockade. This syndrome is partially related to hypergastrinemia, which can be demonstrated in gastric segment diversions. Ulceration is another possible problem with these segments.

6. Mechanical considerations

a. Neuromuscular activity

Bowel segments have an intrinsic coordinated contractile activity that must be taken into consideration when constructing conduits. It is a physiologic property that is disadvantageous for the active storage of urine. For continent reconstruction, the splitting of bowel on its antimesenteric border and its reconfiguration are meant to cause a zero net resultant pressure vector, thus preventing directional flow of urine. Additionally, a general discoordination of contraction activity occurs and thus lowers intraluminal pressure. This discoordination is the primary mechanical effect of reconfiguration, but its long-term efficacy is questionable because several studies suggest the return of coordinated activity fronts over time.

b. Geometric aspects

Much of the effectiveness in creating high-volume, low-pressure reservoirs by bowel reconfiguration may be accomplished by the fact that detubularization essentially approximates a sphere. This is the maximized volume for a given surface area, and the sphere has a larger radius than the tube of the bowel. The law of Laplace states that for a given wall tension, a larger radius will result in lower intraluminal pressure, which is the goal of a continent pouch with regard to continence and the prevention of upper tract deterioration.

to technique and the use of ureteral diversion stents in the perioperative period. Ureteral stenosis is not uncommon and may require balloon dilation or reanastomosis.

b. Colon conduit

A portion of colon may be employed as a urinary conduit. The potential for hyperchloremic acidosis exists but is reduced if short segments of colon are used. When employed in conjunction with a full pelvic exenteration, a bowel anastomosis may be avoided. A transverse colon conduit is a very useful alternative in patients with heavily irradiated bowel. This segment is usually away from most radiation fields and provides a healthy alternative to possibly damaged ileum. Nonrefluxing ureteral anastomoses may be constructed with the use of tinea coli, but the potential for ureteral obstruction exists.

c. Jejunal conduit

The jejunum has been employed as an alternative segment in cases of radiated bowel. Due to its permeability characteristics, it is prone to severe metabolic complications previously described and is not generally employed in urinary diversion.

d. Cutaneous ureteral diversion

This is a direct form of urinary diversion generally complicated by stenosis at the level of the skin and by potential difficulties with collection appliances.

3. Continent urinary diversion
   a. General goals
      1) Adequate capacity reservoir
      2) Low-pressure reservoir
      3) Urinary continence during normal activities
      4) Volitional emptying
   b. General construction
      1) Cutaneous urinary diversion
      2) Orthotopic urinary diversion
   c. Continence mechanisms
      1) Intussuscepted nipple valve
      2) Fixed resistance
      3) Flap valve—Mitrofanoff principle
      4) Pelvic floor external sphincter (orthotopic)
   d. Ureterosigmoidostomy

This is one of the original forms of urinary diversion and can be considered continent urinary diversion in the broad sense. It is rarely applied in developed countries because of the metabolic and neoplastic complications previously described. Recent modifications of this procedure have included J-pouch alteration of the sigmoid colon or the use of detubularized ileal patches to increase local capacity and decrease tenesmus.

e. Cutaneous continent diversion

In this form of diversion, a reservoir or ileum, a colon, or a combination of both is constructed from detubularized bowel and brought to the skin as a discrete, flush, catheterizable stoma. The site may be paraumbilical or just above the pubic hairline. In the case of a thick or distorted abdominal wall, the umbilicus is the preferred site. The site must be catheterized every 4 to 6 hours to avoid over distention. In addition to the standard complications of urinary diversion, patients may develop eccentricity of the catheterization pathway or incontinence requiring revision of the site. Initial series reported revision rates of 25% to 30% but these have decreased to a 5% to 15% range.

1) Indiana pouch: A detubularized segment of cecum and colon acts as a storage reservoir whose continence is maintained by fixed resistance established at the ileocecal valve and distal ileum. The tapered distal ileum serves as the catheterizable limb. Ease of construction and a low complication profile make this a popular form of diversion. Capacity is lower than that seen with ileal pouches, and a potential for chronic diarrhea exists (5%) because of the removal of the ileocecal valve and colonic tissue.
2) Penn pouch: In this form of diversion, the appendix is used in a tunneled method and acts as a flap valve (Mitrofanoff principle) to provide urinary continence. This recapitulates the natural course and mechanism of the ureter as it enters the bladder. Issues of pouch capacity and diarrhea are similar to those seen in the Indiana pouch. The appendix may not be a suitable catheterizable limb in all adults.
3) Monti procedure: The use of a transversely tubularized bowel segment (TTBS) increases the range and flexibility for the construction of a catheterizable limb in a cutaneous continent urinary reconstruction. A 2.5-cm segment of small bowel can be detubularized and transversely retubularized to create long, relatively narrow

bowel segments, which can be implanted in a urinary reservoir and brought to the skin. When necessary, two segments can be attached in series to gain additional length. This is an extension of the Mitrofanoff principle, which uses a small-diameter tube implanted in a flap-valve fashion to provide continence.

4) Pouch hygiene: As previously stated, forms of urinary diversion are subject to bacterial colonization. In continent reservoirs, this may proceed to frank pouchitis and pyelonephritis if emptying is inefficient or incomplete. Furthermore, most bowel segments continue to produce mucus for at least 1 year, which can be a source of obstruction leading to dysfunction and infection. The potential for such difficulties can be reduced by simple maneuvers such as daily pouch irrigation with saline solution by the patient after a routine catheterization.

f. Orthotopic continent diversion

This is a form of continent reconstruction based on the striated external sphincter as the primary continence mechanism. A high-capacity, low-pressure system is essential for an optimal result. Potential complications include enuresis in 5% to 10% of patients (because of relaxation of the pelvic floor during deep stages of sleep) and tumor recurrence at the urethral margin necessitating major surgical revision. Pouches may be constructed of pure ileum (hemi-Kock pouch, ileal neobladder) or mixed segments of large and small bowel (Mainz pouch).

1) Urodynamics: Functional studies reveal excellent capacity, storage, and efficient emptying with a combination of pelvic floor relaxation and abdominal straining. The potentially large capacity of these pouches can make a patient inattentive to the need for voiding. If the reservoir is chronically overdistended, the ability to empty is compromised and may necessitate the need for intermittent catheterization. Upper tract deterioration is primarily avoided by having low static pressures in the pouch and avoiding pouch-ureter reflux. Reflux may be further prevented by an intussuscepted nipple.

2) Female orthotopic diversion: The technique of orthotopic diversion has recently been extended to female patients. Careful pathologic studies have suggested that the absence of CIS or lack of tumor involvement

in the trigone or bladder neck is associated with a lack of tumor in the female urethra. Although a concern for urinary incontinence was an initial issue, it has been noticed that many of these patients will develop partial or complete urinary retention. Patients tend to be equally divided: one third void normally with or without occasional catheterization, one third experience complete urinary retention, and one third have stress urinary incontinence. No significant problems with urethral recurrence have been reported.

## TREATMENT OF ADVANCED DISEASE

1. Chemotherapy for metastatic disease

Urothelial cancer is a moderately chemotherapy-sensitive malignancy. Prognostic risk factors (sometimes called the Bajorin risk factors) for patients with metastatic disease include: visceral metastases (bone, lung, liver); and Karnofsky performance status less than 80% (greater than ECOG 2). Patients are classified as having zero, one, or two risk factors. Patients with zero risk factors treated with cisplatin-based chemotherapy have a median survival of 33 months, and some derive long-term benefit from chemotherapy. Patients with two risk factors have a median survival of 9 months and are unlikely to derive long-term benefit from chemotherapy. An important point is that results of chemotherapy trials including response rate and survival are clearly influenced by patient selection; randomized trials should stratify for these risk factors.

MVAC is the historic standard of care. MVAC is associated with significant toxicity. The combination of gemcitabine and cisplatin has been demonstrated to result in similar survival but with less toxicity than MVAC. A regimen of dose-intense MVAC has not demonstrated improved survival over standard-dose MVAC.

Because cisplatin is nephrotoxic, this agent should not be used in patients with significant renal impairment. Approximately one quarter of patients with advanced urothelial cancer are not candidates for cisplatin because of renal insufficiency. The combination of paclitaxel plus carboplatin can be used in these patients but has less therapeutic efficacy.

There is no standard effective second-line chemotherapy option for patients with advanced urothelial cancer. Patients should be encouraged to participate in clinical trials investigating novel agents.

2. Neoadjuvant and adjuvant chemotherapy

Patients with muscle-invasive bladder cancer are at risk of developing metastatic disease, even after cystectomy. Postcystectomy pathology demonstrating extravesical disease or lymph node metastases is associated with an increased risk of recurrence and distant metastases. Systemic chemotherapy has been studied to determine if it can eradicate micrometastatic disease in the earlier disease setting.

Neoadjuvant chemotherapy refers to chemotherapy given before cystectomy. A meta-analysis of multiple randomized trials demonstrated that neoadjuvant chemotherapy is associated with an absolute survival advantage of about 5% at 5 years. Neoadjuvant therapy can also be given to downstage locally advanced tumors.

Adjuvant chemotherapy refers to systemic chemotherapy administered after cystectomy. Small trials suggest benefit, but a sufficiently powered randomized trial of surgery alone versus surgery plus adjuvant chemotherapy has not been performed.

Finally, a small trial from MD Anderson Cancer Center compared neoadjuvant MVAC with adjuvant MVAC and determined that survival was similar with both approaches.

## CLINICAL PEARLS

***Bladder Cancer***

- Tobacco use confers a two- to threefold increased risk of developing bladder cancer.
- Stage and grade are both significant predictors of recurrence and progression in bladder cancer.
- Hematuria in some form is noted in 85% of cases of bladder cancer.
- Intravesical BCG therapy has an initial clinical response rate of 60% to 80% for CIS.
- Neoadjuvant chemotherapy is associated with a 5% absolute survival advantage for patients with muscle invasive bladder cancer.

## DIFFERENTIAL DIAGNOSIS

***Elevated PSA***

- BPH
- Prostate cancer
- Prostatitis
- Recent urologic instrumentation
- Recent ejaculation
- Urinary tract infection

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Has the case for prostate cancer screening and disease detection been proven?*
2. *What are the principal issues that should be considered by the physician and patient in the choice of therapy for clinically localized bladder cancer?*
3. *What are the side effects of androgen blockade therapy?*
4. *What are the alternatives for the treatment of high-grade T1 bladder cancer?*
5. *Describe the general complications of urinary diversion.*

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## CHAPTER 17

# Adult Genitourinary Cancer: Renal, Testicular, and Penile

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## Neoplasms of the Kidney

### GENERAL CONSIDERATIONS

The paradigm in diagnosis, evaluation, and management of renal cell carcinoma (RCC) has evolved significantly over the last several decades. Whereas 30 years ago the diagnosis of RCC was predicated on clinical signs and symptoms, the **majority of renal tumors are now diagnosed incidentally on imaging performed for other reasons.** The identification of iatrogenic renal insufficiency associated with radical nephrectomy has rendered nephron-sparing techniques the preferred treatment for small renal masses. Active surveillance of small renal masses has also emerged as an option for select patients. Although RCC remains the prototype for tumors resistant to radiation and chemotherapy, an expanding number of molecular targeted therapies are now available.

### INCIDENCE AND EPIDEMIOLOGY

There will be approximately 63,150 new cases of RCC in 2013 and 13,680 deaths attributable to the disease. **The incidence of RCC has increased over the last several decades with a stage migration towards lower-stage, smaller tumors.** Despite this downward stage migration, there has yet to be a demonstrable decrease in kidney cancer-related mortality rates.

RCC represents 5% of all male cancers and 3% of all female cancers, with a male-to-female ratio of 3:2 and a peak incidence in the sixth to seventh decade of life. Most RCC cases are sporadic, but a number of hereditary conditions are associated with various renal tumors (Table 17-1). In general, RCC in hereditary syndromes have an autosomal-dominant inheritance pattern with variable penetrance. RCCs associated with hereditary syndromes generally present at an earlier age and are more likely to be bilateral and multifocal. Although these hereditary conditions are uncommon (2% to 3% of all patients with RCC), they have been essential in improving RCC tumor biology.

## ETIOLOGY

**Tobacco use is the strongest known risk factor for RCC, with users having an approximately twofold increased risk**. Hypertension and obesity have also been associated with RCC in large epidemiologic studies. Furthermore, increased incidence of RCC has been reported in patients with acquired renal cystic disease secondary to end-stage renal disease (ESRD)/dialysis. Given this observed increased risk, many practitioners advocate performing periodic imaging in dialysis patients.

## PATHOLOGY: RENAL TUMORS

1. RCC
   a. RCC represents nearly 80% of solid renal tumors. Several distinct histologic patterns have been observed. The most common histopathologic entities are clear cell (conventional) RCC followed by papillary RCC. Both are thought to arise from the proximal convoluted tubular epithelium. Less commonly observed are chromophobe RCC and collecting duct carcinoma, which arise from components of the distal nephron. Other rare subtypes are also recognized. Sarcomatoid differentiation occurs in up to 5% of RCC, may be present with any subtype, and carries significant negative prognostic value.

      Grossly, RCC is usually round and contained within a fibrous pseudocapsule. Most sporadic tumors are solitary and unilateral, but up to 5% of patients will develop bilateral tumors. RCC has a unique predilection for venous involvement, with up to 10% harboring tumor thrombus at presentation.

   b. Clear cell (conventional) RCC: **This is the most common histology accounting for 70% to 80% of all RCC. It is associated with an allelic loss of the VHL gene**. Grossly, tumors appear yellow or gray-tan in color with variable areas of hemorrhage, necrosis, or cystic changes. Microscopically,

TABLE 17-1 **Hereditary Syndromes Associated with RCC**

| Syndrome Name | Gene Involved | Renal Tumors | Other Manifestations |
|---|---|---|---|
| Von Hippel-Lindau (VHL) disease | VHL gene (3p25-26) | Clear cell RCC in 50% of patients (also type 1 papillary RCC) | Cysts of the epididymis and pancreas, cerebellar hemangioblastomas, retinal angiomas, and pheochromocytoma |
| Hereditary papillary RCC | c-MET proto-oncogene (7q31) | Type 1 papillary RCC | None described |
| Hereditary leiomyomatosis and RCC | Fumarate hydratase (1q42) | Type 2 papillary RCC | Cutaneous and uterine leiomyomas |
| Birt-Hogg-Dubé syndrome | BHD1 gene/folliculin (17p12q11) | Chromophobe RCC, oncocytoma, hybrid oncocytic cells (also clear cell RCC seen) | Cutaneous fibrofolliculomas, lung cysts with spontaneous pneumothorax |
| Tuberous sclerosis complex (TSC) | TSC1/TSC2 tuberin | Angiomyolipomas (AML; 60%-80% of patients), renal cysts (20%-30% of patients), RCC (<1%) | Facial angiofibroma, subependymal nodules epilepsy, mental retardation, |

they are composed predominantly of cells with clear eosinophilic or granular cytoplasm. In general, clear cell RCC has a worse prognosis than papillary and chromophobe RCC after adjustment for grade and stage.

c. Papillary RCC: This comprises 10% to 15% of newly diagnosed RCC, but accounts for a higher percentage in patients with end-stage and acquired renal cystic disease. Papillary RCC is more likely to be multifocal or bilateral than other histologies. Two distinct subtypes are recognized: Type 1 and Type 2 papillary RCC. They are associated with two different familial RCC syndromes (see Table 17-1). Papillary type 1 tumors are associated with activation of the *MET* proto-oncogene (chromosome 17), whereas papillary type 2 tumors are associated with mutations in the fumarate hydratase gene. Type 2 papillary RCC tends to be the more aggressive variant.
d. Chromophobe RCC: This represents 3% to 5% of RCC and is associated with multiple chromosome losses. Histologically, a defining feature is its perinuclear “halo.” Chromophobe RCC histology may be confused with oncocytoma, a benign renal lesion. Chromophobe RCC tends to have a better prognosis than clear cell and papillary subtypes.
e. Collecting duct carcinoma: This is a rare but very aggressive RCC subtype, representing less than 1%. It tends to occur in younger patients, and up to half have metastasis at presentation.
f. Renal medullary carcinoma: This is a highly aggressive tumor seen in young black Americans with sickle cell trait. It may represent a variant of collecting duct carcinoma and carries a very poor prognosis.

2. Oncocytoma

Accounting for approximately 5% of all renal tumors, oncocytomas are well-circumscribed parenchymal masses composed of densely acidophilic cells that show mitochondrial hyperplasia on electron microscopy. They may be bilateral in up to 5% of cases. In contrast to RCC, the principal genetic alteration appears to involve changes in mitochondrial DNA and translocation of chromosome 14. Grossly, they are mahogany brown in color, encapsulated, and may contain a dense central scar extending in a stellate pattern, which may be identified in cross-sectional imaging. Oncocytomas are benign and can be managed conservatively; however, their preoperative clinical diagnosis is often unreliable, and a definitive diagnosis may be made on frozen section or percutaneous biopsy due to histologic similarities to chromophobe RCC.

3. Angiomyolipoma (AML)

   These benign lesions composed of fat, muscle, and blood vessels can generally **be identified by the presence of macroscopic fat on CT scan**. Although lesions are generally identified as incidental radiographic findings, patients may present with acute flank pain or hemorrhagic shock due to spontaneous renal or retroperitoneal hemorrhage. Treatment is based on tumor size and patient symptoms. **Asymptomatic tumors smaller than 4 cm may be managed expectantly. However, symptomatic tumors or those greater than 4 cm should undergo selective embolization, percutaneous ablation, or nephron-sparing surgery**. Some large central tumors not amenable to nephron-sparing strategies may require radical nephrectomy. Recently, mammalian target of rapamycin (mTOR) inhibitors have been shown to decrease the size of AML and may be a promising therapy for patients with multiple lesions.

4. Sarcoma

   Sarcomas constitute 2% to 3% of malignant renal parenchymal tumors. They are more common in women. Differentiation from RCC is difficult. The predominant subcategory is leiomyosarcoma. The preferred treatment remains radical nephrectomy with wide negative margins.

5. Lymphoma

   B-cell non-Hodgkin lymphoma will occasionally present as an infiltrative renal mass. It is uncommon for leukemia to present as a primary renal lesion.

6. Metastasis

   The most common metastases to the kidneys are primary carcinomas of the lung, breast, and uterus, and melanoma. Metastatic lesions appear poorly vascularized and display irregular borders on imaging studies. A percutaneous biopsy of the renal mass may be warranted in patients with signs of progression from their other malignancy or in masses that do not demonstrate contrast enhancement on imaging studies.

## GRADING AND STAGING

The Fuhrman grading system is commonly used to classify nuclear features of RCC. It ranges from Grade I (well differentiated) to IV (poorly differentiated) and is contingent on nuclear size, nuclear outline, and presence of nucleoli. The most common staging system for RCC remains the American Joint Committee on Cancer (AJCC) TNM system (Table 17-2). Major changes occurred in the tenth edition, including subdivision of T2 tumors

TABLE 17-2 **AJCC 7th Edition Staging System for Renal Cell Carcinoma**

***Primary Tumor (T)***

TX - Primary tumor cannot be assessed
T0 - No evidence of primary tumor
T1 - Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a - Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b - Tumor >4 cm but not >7 cm in greatest dimension, limited to the kidney
T2 - Tumor >7 cm in greatest dimension, limited to the kidney
T2a - Tumor >7 cm but 10 cm or less in greatest dimension, limited to the kidney
T2b - Tumor >10 cm, limited to the kidney
T3 - Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
T3a - Tumor grossly extends into renal vein or segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia
T3b - Tumor grossly extends into the vena cava below the diaphragm
T3c - Tumor grossly extends into the vena cava above the diaphragm or invades into the wall of the vena cava
T4 - Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

***Regional Lymph Nodes (N)***

NX - Regional lymph nodes cannot be assessed
N0 - No regional lymph node metastasis
N1 - Metastasis in regional lymph node

***Distant Metastasis (M)***

M0 - No distant metastasis
M1 - Distant metastasis

*(From Edge SB, Byrd DR. Compton CC, et al, editors:* AJCC cancer staging manual*, ed 7, New York, 2010, Springer.)*

and reclassification of tumors with lymphatic involvement, tumor thrombus, and adrenal metastasis. **Pathologic stage remains the single most important prognostic factor**. Other important considerations are tumor size, grade, subtype, presenting symptoms, and patient factors. Whereas 5-year survival for patients with T1a disease is between 90% and 100%, survival drops to 50% to 70% in patients with T3a disease, and to 20% or less in patients with nodal or distant metastatic disease.

## CLINICAL PRESENTATION

**Greater than 50% of all RCCs are found as asymptomatic incidental masses on imaging studies obtained for another purpose**. The classic triad of hematuria, flank pain, and a palpable mass was historically seen in approximately 10% of patients but is now a rare presentation. Systemic symptoms of unintentional weight loss, fever, anemia, and night sweats suggest the presence of metastasis. Tumor thrombus can obstruct drainage of the testicular vein, producing a right-sided or noncollapsible varicocele. Paraneoplastic syndromes may occur in advanced disease, including hypercalcemia from parathyroid-like hormone production, hypertension, polycythemia, and Stauffer syndrome, or nonmetastatic hepatic dysfunction.

## IMAGING EVALUATION

The most common renal mass is a benign cyst, identified in approximately 50% of patients over 50 years of age. A mass not meeting ultrasound criteria for a simple cyst should be evaluated with a dedicated renal CT scan or MRI with thin cuts. Renal cysts are classified by the Bosniak system (Table 17-3).

1. Diagnostic studies
    a. CT: Precontrast and postcontrast thin-slice CT images should be obtained. Contrast-enhanced imaging takes advantage of the neovascularity of most renal neoplasms. **Enhancement of greater than 15 Hounsfield units is worrisome, and the presence of enhancement must prompt immediate consideration of RCC**. The presence of macroscopic fat, defined as regions of attenuation of less than –20c Hounsfield units, indicates the presence of AML. In addition to characterizing the primary renal tumor, CT provides information on lymph node involvement, perinephric extension, and venous

TABLE 17-3 **Bosniak Classification of Cystic Masses**

| Category | Description | Risk of Malignancy |
|---|---|---|
| Bosniak I | Simple cyst; measuring water density; does not enhance; contains no calcifications | <2% |
| Bosniak II | Minimally complex cyst; thin wall (<1 mm); no enhancement, although may contain several hairline septa; hyperdense cyst | <5% |
| Bosniak IIF | Indeterminate; complex cyst with thicker septa | ~25% |
| Bosniak III | Suspicious indeterminate; thicker, regular, nodular walls with thicker, regular calcifications and septations | ~50% |
| Bosniak IV | Malignant; nodular or solid component | >90% |

involvement. High-speed spiral CT technology permits 3D renal reconstruction and CT angiography, which may be very useful in preparation for either nephron-sparing surgery or laparoscopic renal surgery.

b. Renal ultrasound: Ultrasound is an inexpensive and noninvasive modality used to distinguish cystic from solid renal masses. A simple cyst will be smooth with a definite border of imperceptible thickness, be absent of internal echogenicity, and should display acoustic enhancements beyond the posterior wall.

c. MRI: This is an alternative to CT for evaluation of renal masses and is particularly useful for those with iodinated contrast allergies. Enhancement seen after gadolinium contrast on T1-weighted images is characteristic of RCC. MRI is also effective in demonstrating the presence and extent of renal vein or vena caval tumor thrombi. Whereas contrast-enhanced MRI was historically performed in patients with renal insufficiency, it is now avoided because of the risk of nephrogenic systemic fibrosis with gadolinium administration in patients with chronic kidney disease (CKD).

   d. Angiography: Classic angiography has been largely replaced by magnetic resonance angiography or 3D CT angiography in the evaluation of the renal vessels. However, renal angioembolization may be useful before radical nephrectomy for very large central tumors or in the presence of bulky hilar adenopathy.
   e. Radionuclide imaging: This may be useful in determining the presence of a pseudotumor. Renal pseudotumors can results from multiple causes, but the most common is hypertrophied column of Bertin. Pseudotumors appear with a uniform distribution of radioisotope uptake on radionuclide imaging, whereas benign cysts and true renal tumors will appear as photon-deficient areas of uptake.
   f. Percutaneous biopsy: Historically, biopsy was performed only if a renal mass was suspected to be lymphoma, metastasis, or abscess. In recent years, percutaneous biopsy has been revisited. Nearly one third of small renal masses are benign, and the majority of the remaining two thirds are frequently low-grade tumors. Most contemporary series show greater than 90% accuracy with biopsy, with complication rates less than 2%. Biopsy provides valuable information on grade and histologic subtype, both of which can be used for treatment planning.
2. Clinical staging

   The initial workup and clinical staging, according to the National Comprehensive Cancer Network (NCCN) guidelines, consists of a history, physical exam, complete blood count, comprehensive metabolic panel, urinalysis, chest imaging, and a contrast-enhanced cross-sectional imaging of the abdomen and pelvis. A bone scan may be obtained in symptomatic patients or those with elevated alkaline phosphatase. If neurologic symptoms or extensive metastatic disease is present, a brain MRI should be considered. For renal masses that are suspicious for urothelial origin, dedicated urothelial imaging (including urogram or pyelograms), urinary cytology, and ureteroscopy should be considered.

## TREATMENT

1. Small renal masses and localized disease (T1-T2)
   a. Surgical management

   A dramatic change in the treatment of clinical T1 renal masses has occurred over the last several years. At one time nephron-sparing surgery (NSS) was reserved only for those with absolute indications, including preexisting renal insufficiency or solitary kidney. With improvements in our understanding of the risk of CKD following radical nephrectomy, **NSS has emerged as the preferred treatment for small renal masses**. Most studies demonstrate similar oncologic outcomes with greater preservation of renal function with partial nephrectomy compared to radical nephrectomy. Local recurrence rates are less than 5%. Furthermore, several series have shown that tumor enucleation can maximize parenchymal sparing and still provide adequate oncologic outcomes. The operative morbidity of partial nephrectomy is similar to radical nephrectomy, but with the potential for slightly greater blood loss and urinary leak. Renal ischemia remains a concern during partial nephrectomy. Ischemia can be avoided in select cases by not clamping or selectively clamping segmental arteries. Renal cooling is used to convert warm ischemia to cold ischemia, thereby decreasing the metabolic rate of the kidney with the goal of avoiding acute tubular necrosis (ATN). Although ischemic time is important, **the amount of renal parenchyma that is preserved is the most important factor that the surgeon can modify for long-term renal function preservation.**

**Radical nephrectomy is now generally reserved for large tumors or tumors not amenable to partial nephrectomy**. Approximately 25% of all clinical T2 tumors will have perinephric fat invasion, best treated with radical nephrectomy. Components of radical nephrectomy include early vascular ligation and en bloc removal of the kidney, surrounding Gerota fascia, and proximal ureter. Recent data suggests that ipsilateral adrenalectomy is unnecessary in the presence of a normal-appearing adrenal gland that does not appear to be involved radiographically or intraoperatively.

The role of lymphadenectomy at the time of renal surgery remains poorly characterized. It may provide a small benefit in controlling micrometastatic disease in select patients, but a well-performed randomized trial failed to show any survival benefit attributable to the routine application of lymphadenectomy. The surgical approach to a renal mass depends on tumor and patient characteristics but also upon surgeon experience. Laparoscopic partial and radical nephrectomy can be performed using a transperitoneal or retroperitoneal approach with pure laparoscopy, hand-assistance, or robotic assistance.

   b. Tumor ablative techniques

      Percutaneous or laparoscopic ablation using cryosurgery or radiofrequency offers reduced morbidity and more rapid recovery when compared to surgical excision. These benefits, however, are balanced with higher rates of local recurrence. Between-series comparisons are difficult because reliable histologic and pathologic staging is not performed with ablative techniques. Long-term efficacy has yet to be established, and, as such, ablation is typically reserved for patients of advanced age and significant comorbidity. Tumor size is also an important predictor of success; therefore ablative therapy is generally reserved for renal masses less than 4 cm.

   c. Active surveillance

      With the increasing number of incidentally identified renal masses, particularly in comorbid elderly patients, active surveillance for small renal masses has emerged as a reasonable management strategy. The median growth rate for most small renal masses is less than 0.3 cm/year, and, for biopsy-proven RCC, it is only approximately 0.4 cm/year. Tumors less than 3 cm may be monitored with serial imaging every 6 to 12 months. Increased growth kinetics and surpassing a size threshold are typical indications for intervention. Early series demonstrate a low risk of metastatic dissemination in small renal masses under active surveillance.

2. Locally advanced RCC
   a. Inferior vena caval tumor thrombus: Inferior vena cava extension occurs in 4% to 10% of patients with newly diagnosed RCC, more commonly in patients harboring clear cell RCC. In the absence of vascular wall invasion or metastasis, an aggressive surgical approach with nephrectomy and tumor thrombectomy is advocated. Advanced surgical techniques can be successful, usually with thoracoabdominal, chevron, or midline approaches to permit complete vascular control. Cardiopulmonary bypass with or without hypothermic cardiac arrest can be used for bulky intrahepatic or suprahepatic lesions. MRI, multiplanar CT scan, or transesophageal echocardiography (TEE) should be performed as close to surgery as possible to evaluate the extent of the thrombus because progression can affect the surgical approach. Operative mortality ranges from 1.4% to 14%, with 30% to 40% postoperative complications such as sepsis, retroperitoneal hemorrhage, or hepatic dysfunction.

   b. Adjuvant systemic therapy: No studies of adjuvant systemic therapy after nephrectomy for high-risk patients have demonstrated a survival advantage. These trials have been limited by patient accrual.

3. Metastatic RCC
   a. Motzer criteria: Patients with metastatic disease can be categorized into low, intermediate, and poor risk based upon published criteria. Such criteria include metastasis-free interval from nephrectomy, performance status, number and location of metastases, and select laboratory values. Often referred to as the Motzer criteria, this risk-stratification scheme was initially described in patients receiving immunotherapy but has recently been validated in patients receiving vascular endothelial growth factor (VEGF)–targeted therapy.
   b. Cytoreductive nephrectomy: The role for radical nephrectomy in patients with metastatic RCC in the current era of targeted systemic therapy remains largely unknown. Historically, cytoreductive nephrectomy was performed in individuals with an excellent performance status undergoing immunotherapy. Randomized trials have demonstrated a benefit of nephrectomy and immunotherapy compared to immunotherapy alone; however, no such trials have been reported in patients receiving targeted therapy.
   c. Metastasectomy: Approximately 1% to 4% of patients with metastatic disease will have a solitary metastasis or oligometastasis, for which surgical resection provides a 5-year survival between 30% and 50%.
   d. Systemic therapy: The chemo-refractory nature of RCC likely arises from the expression of multidrug resistance efflux pump proteins. RCC is, however, an immunogenic tumor, and the use of immunotherapy was the cornerstone of systemic therapy for many years. Interferon alpha provides a 15% partial response rate, but complete response is very rare; therefore it is no longer commonly used. High-dose interleukin-2 remains the only treatment associated with durable, complete response with long-term survival in select patients. A response rate in the 10% to 20% range has been demonstrated, but treatment is associated with major toxicities, including adult respiratory distress syndrome

(ARDS) as a result of the capillary leak syndrome. Some centers still offer high-dose interleukin-2 to young patients with good performance status who have metastatic clear cell RCC. Inpatient admission, frequently to ICU-level settings, is required during administration to monitor for toxicity and provide supportive care.

In recent years, efforts have focused on leveraging knowledge of the molecular mechanisms by which RCC develops. This has led to the usage of molecular targeted therapies that inhibit angiogenesis and cell cycle regulation. Tyrosine kinase inhibitors (TKIs) that target VEGF-mediated pathways are most commonly used. Sunitinib was originally used in immunotherapy refractory patients but now is most commonly used instead of immunotherapy as a first-line agent. Sorafenib, another tyrosine kinase inhibitor that is thought to be more promiscuous with the receptors it targets, is frequently given as a second-line agent after progression on a first TKI. Additional kinase inhibitors are now available; however, the optimal sequencing of these agents is unknown. Everolimus is an mTOR inhibitor reserved as a second-line therapy for patients refractory to tyrosine kinase inhibitors. Temsirolimus, another mTOR inhibitor, is approved for poor-risk metastatic RCC. Using RECIST criteria, multiple studies have revealed fairly consistent response rates to various TKIs, on the order of 30% to 40%. Despite the fact that these agents are largely well-tolerated and provide satisfactory disease control, there have been few long-term responses to TKI therapy. Further investigation of combination therapy is ongoing.

## FOLLOW-UP AFTER TREATMENT

Practice patterns for RCC follow-up vary dramatically between centers. Because cross-sectional imaging is usually required, cost and radiation exposure can vary widely between surveillance protocols. The NCCN recommends a history, physical, and comprehensive metabolic panel every 6 months for 2 years, then annually for 5 years. According to the NCCN, imaging of the chest, abdominal, and pelvis should be obtained 2 to 6 months from treatment and then only as indicated. The authors advocate for an individualized approach based on patient and tumor characteristics.

# Urothelial Tumors of the Renal Pelvis and Ureter

## GENERAL CONSIDERATIONS

The urinary tract is lined by urothelial cell epithelium from the most proximal calyces to the proximal urethra. In this section, attention is given to the tumors of the renal collecting system and the ureter. It is essential that urothelial tumors of the renal pelvis and ureter be understood in the broad context of urothelial cell carcinoma (UCC), which is discussed in greater detail in the section on bladder cancer. Although UCC of the upper tract shares similarities to urothelial carcinoma of the bladder (UCB), several distinct differences merit consideration.

## INCIDENCE

Upper tract UCC (UTUCC) accounts for 5% to 7% of all renal tumors and 5% to 10% of all urothelial cancers. The exact incidence of UTUCC is largely unknown because renal pelvis tumors are generally included in data on all renal tumors. It is estimated that there will be 2,710 new cases of ureteral UCC in 2013 with 900 deaths attributable to the disease. Although the incidence of **UTUCC is thought to be increasing over the last several decades, it remains a rare tumor type. Patients with a history of UCB have a 2% to 4% chance of developing upper tract tumors (synchronous or metachronous); however, this increases up to 25% in patients with carcinoma in situ (CIS) of the bladder or in patients with high-grade tumors adjacent the ureteral orifices. Following radical cystectomy, an approximately 7% chance of developing UTUCC exists, with the preponderance of this risk being in the first 3 to 4 years after cystectomy**. Patients with high-grade nonmuscle-invasive bladder cancer should undergo routine upper tract surveillance, given the increased risk of developing upper tract disease. Nonetheless, the optimal intensity of upper tract surveillance remains largely unknown. It is the authors' practice to perform upper tract surveillance every 1 to 2 years in high-risk patients. Conversely, patients with a history of an incident upper tract tumor have a 15% to 50% chance of eventually developing UCB. For this reason, routine surveillance cystoscopy is necessary in all patients with UTUCC. Metachronous bilateral UTUCC occurs in 2% to 4% of patients with UTUCC.

## ETIOLOGY AND NATURAL HISTORY

As in UCB, chemical carcinogenesis is the most important factor in the development of UTUCC. Because of the relatively short transit time of urine through the upper tracts, lesions of the upper tract occur much less often than bladder lesions. Similarly, distal ureteral tumors are more common than proximal. Ureteral UCC occurs in the distal, mid, or proximal ureter in 70%, 20%, and 5% of cases, respectively.

**Similar to UCB, the most common risk factor is smoking. Tobacco use is associated with at least a twofold increase in the relative risk for the disease, but this risk may be up to sevenfold higher in long-term, heavy smokers.** An uncommon but notable risk factor for the development of UTUCC is Balkan nephropathy, an inflammatory lesion of the renal interstitium endemic to the Balkan region. Balkan nephropathy is characterized by multiple, often bilateral, low-grade upper tract urothelial tumors that may be associated with aristolochic acid intake. Abuse of phenacetin, an analgesic medication withdrawn by the FDA, is considered a historical risk factor for the disease. A few hereditary conditions are associated with UTUCC, including Lynch syndrome II, which is characterized by the early development of nonpolyposis colonic tumors and additional extracolonic neoplasms.

**Depth of invasion is the single most important prognostic factor in UTUCC 5-year survival ranges from 100% for noninvasive tumors (Ta) to 40.5% for tumors invading beyond the muscularis (T3).** Because of the relative paucity of muscle wall thickness compared to the bladder, UTUCC is considered more likely to be of advanced stage at presentation. Interestingly, the renal parenchyma is thought to prevent spread of T3 tumors in the renal pelvis compared to UTUCC in the ureter.

## CLINICAL PRESENTATION

Sixty percent to 98% of patients present with either microscopic or gross hematuria. Flank pain can occur in up to 30% of patients, which may be due to obstruction secondary to tumor, blood clot, or a combination of both. Only 15% of UTUCC is identified incidentally; however, these tumors are likely to manifest clinically because UTUCC is rarely discovered at autopsy.

TABLE 17-4 **AJCC 7th Edition Staging System for Upper Tract Urothelial Carcinoma**

***Primary Tumor (T)***

TX - Primary tumor cannot be assessed
T0 - No evidence of primary tumor
Ta - Papillary noninvasive carcinoma
Tis - Carcinoma in situ
T1 - Tumor invades subepithelial connective tissue
T2 - Tumor invades the muscularis
T3 - Renal pelvis tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
T3 - Ureter tumor invades beyond muscularis into periureteric fat
T4 - Tumor invades adjacent organs or through the kidney into perinephric fat

***Regional Lymph Nodes (N)****

NX - Regional lymph nodes cannot be assessed
N0 - No regional lymph node metastasis
N1 - Metastasis in a single lymph node 2 cm or less in greatest dimension
N2 - Metastasis in single lymph nodes >2 cm but not >5 cm in greatest dimension; or multiple lymph nodes, none >5 cm in greatest dimension
N3 - Metastasis in a lymph node >5 cm in greatest dimension

***Distant Metastasis (M)***

M0 - No distant metastasis
M1 - Distant metastasis

*Note: Laterality does not affect the N classification.

*(From Edge SB, Byrd DR. Compton CC, et al, editors:* AJCC cancer staging manual, *ed 7, New York, 2010, Springer.)*

## PATHOLOGY AND STAGING

UTUCC and UCB share common pathologic subtypes. The TNM staging systems for UTUCC is analogous to that of UCB (Table 17-4). However, clinical staging in UTUCC is extremely difficult given the technical challenges associated with endoscopic sampling.

## DIAGNOSIS

1. Radiographic studies: UTUCC will appear as a radiolucent filling defect in 50% to 75% of cases. CT urography has become the most commonly used imaging modality to

identify upper tract urothelial tumors. CT urogram can help to differentiate a renal parenchymal mass from a renal pelvic mass, and a ureteral tumor from a radiolucent calculus. Nonetheless, **the distinction between a UTUCC and a central renal parenchymal mass is frequently challenging and commonly requires endoscopic evaluation**. MR urography can be used as a substitute for CT urography in patients unable to receive iodinated contrast. CT and MR urograms provide useful staging information, including the presence of lymphadenopathy, and extent of invasion. Despite this, CT urogram has been shown to misstage nearly 40% of patients.

Prior to the widespread adoption of CT urography, intravenous excretory urography (IVU) was commonly used and is still used in some centers. Additionally, retrograde pyelography can be used to evaluate the upper urinary tracts in patients unable to receive intravenous contrast because of CKD. Retrograde pyelograms are also indicated to evaluate pyelocalyceal and ureteral segments not adequately visualized on excretory urography, given the greater sensitivity for the identification of small filling defects.

## DIFFERENTIAL DIAGNOSIS

***Differential diagnosis of upper urinary tract filling defects includes:***

Air
Papilloma
Malakoplakia
Sloughed papilla
Secondary metastasis
Uric acid or matrix calculi
Extrinsic compression (vessels, adenopathy, retroperitoneal fibrosis)
Urinary tuberculosis
Ureteritis or pyelitis cystica
Inverted papilloma
Sarcoma

2. Ureteroscopy: Endoscopic evaluation permits direct visualization and biopsy of the upper tract urothelium. Tumor morphology has some correlation to tumor stage and grade; papillary tumors are more likely to be low grade and noninvasive, whereas sessile tumors are more likely to be high grade and invasive. Urinary cytology is collected prior to biopsy. Given the difficulties in endoscopic sampling,

clinical staging remains a challenge. However, **tumor grade on biopsy has been shown to correlate with risk for invasion and may serve as a surrogate. Low-grade tumors are far less likely to be invasive.** These findings have implications for therapy because small, low-grade lesions are frequently amenable to endoscopic laser ablation.

3. Brush biopsy and cytology: This is usually performed during pyeloureterography and may be done by an urologist or radiologist. Although the combination of an upper tract filling defect and a positive renal wash cytology in the same side is sufficient evidence for definitive surgical treatment, ureteroscopy may identify multifocal tumors. A positive renal cytology in the absence of urothelial filling defects mandates further evaluation with ureteroscopy.

## TREATMENT OF UTUCC

Multiple treatment options exist for patients with UTUCC, and treatment choice should be individualized based upon disease characteristics, baseline renal function, and functional status.

1. Radical nephroureterectomy with excision of a bladder cuff: **Nephroureterectomy remains the preferred treatment for tumors of the renal pelvis and proximal ureter that are large, high grade, and invasive.** Furthermore, nephroureterectomy should be considered for tumors that are not amenable to endoscopic ablation. During radical nephroureterectomy the entire distal ureter, including the intramural portion, should be removed en bloc given the unacceptably high risk of recurrence within a remnant ureteral stump (30% to 60%). Concomitant adrenalectomy may be deferred if preoperative imaging and intraoperative examination reveal the adrenal gland to be normal. The open procedure may be performed via a single thoracoabdominal incision or a two-incision approach (flank and infraumbilical midline).
2. Laparoscopic, hand-assisted-laparoscopic, and robotic-assisted-laparoscopic nephroureterectomy: These minimally-invasive techniques have been popularized and are the preferred approach at many academic and community centers. Although the minimally invasive approach to the kidney is of clear benefit, the laparoscopic management of the bladder cuff remains controversial. Some have advocated that the safest approach

includes bladder cuff excision using an open approach via the kidney extraction incision. This may be performed extravesically or through a transvesical approach. Other approaches to the bladder cuff include complete transurethral resection of the intramural ureter and cauterization with endoscopic stapling. These techniques may reduce operative time and avoid an additional incision; however, there are few high-quality data upon which to evaluate the comparative effectiveness and harms of various techniques. Regardless of technique, it is essential to remove the specimen en bloc within a "closed" system because UCC can implant on nonurothelial surfaces. There have been case reports of trocar site and peritoneal seeding after laparoscopic nephroureterectomy when oncologic principles were violated.

3. Endoscopic management: For low-volume, low-grade tumors, a retrograde ureteroscopic approach is preferred. A percutaneous antegrade approach may be considered for larger tumors in the renal pelvis and proximal ureter, although this is associated with greater morbidity. Regardless of the approach, cytology should be collected and the tumor should be biopsied prior to laser ablation or fulguration. Multiple biopsies are usually required considering the small yield of endoscopic forceps. Although stage cannot be assessed with ureteroscopic biopsies, tumor grade has been found to correlate well with tumor stage. Specifically, approximately 90% of low-grade tumors are found to be noninvasive compared to 30% of high-grade (grade 3) tumors. Greater than 50% of patients suffer recurrence within the ipsilateral collecting system, and, as such, strict surveillance is essential. Over 30% of patients initially managed endoscopically progress to radical nephroureterectomy. These patients do not appear to be at increased risk for metastatic disease compared to those undergoing upfront nephroureterectomy.
4. Ureterectomy: This may be indicated for patients who are not candidates for endoscopic management but who have a compelling indication for nephron-sparing surgery. Ureterectomy can be performed open or with various laparoscopic techniques. Segmental ureterectomy with ureteroureterostomy may be considered for proximal or midureteral tumors; however, the ureter distal to the anastomosis remains at high risk for recurrence. For distal tumors, a complete distal ureterectomy

can be performed with a direct ureteroneocystostomy. If the length of excised ureter is longer, then a psoas hitch with or without Boari flap can be employed. A downward nephropexy has also been used to reduce the distance of the ureteral defect. Less common approaches include subtotal ureterectomy with ileal interposition or renal autotransplantation.

5. Lymphadenectomy: Regional lymph nodes may be removed at the time of radical nephroureterectomy with little additional operative time and minimal morbidity. However, unlike UCB where an adequate lymphadenectomy provides a clear survival benefit at time of radical cystectomy, the therapeutic benefits of lymphadenectomy for UTUCC remain unknown. This may be because the lymphatic drainage for the renal pelvis and ureter is less well defined and dissection boundaries are variable. Lymphadenectomy does provide valuable prognostic information in UTUCC, particularly when considering adjuvant chemotherapy. Node-positive patients almost invariably develop early distant metastasis.
6. Chemotherapy
   a. Intrarenal and intraureteral therapy: Instillation of immunotherapeutic and chemotherapeutic agents has been used in an effort to decrease the risk of ipsilateral recurrence after endoscopic management. The same agents used for UCB are used for UTUCC (bacille Calmette-Guérin [BCG] and mitomycin). However, unlike UCB where improvements in recurrence have been clearly demonstrated, data on the use of intrarenal topical therapy remain sparse. The lack of benefit in UTUCC may be the result of insufficient patients in trials or from inadequate delivery systems to the upper tracts. Agents can be instilled through a nephrostomy tube (often after percutaneous management) or retrograde via ureteral reflux by way of stenting.
   b. Systemic chemotherapy: Similar to UCB, urothelial tumors of the upper tract are chemo sensitive, and the chemotherapy regimens are modeled after those used in UCB. The historical standard for the management of metastatic UCC is methotrexate, vincristine, Adriamycin (doxorubicin), cisplatin (MVAC) chemotherapy, but combination chemotherapy with cisplatin and gemcitabine has proven to be equivalent with respect to efficacy and results in considerably less morbidity. Unfortunately, many patients with UCC are

"unfit" to tolerate cisplatin, largely secondary to baseline renal insufficiency. Radical nephroureterectomy, even more so than radical cystectomy, is likely to reduce renal function, precluding many patients from receiving cisplatin in the adjuvant setting. This has led to increased interest on neoadjuvant cisplatin-based regimens. Prospective trials are ongoing to evaluate the long-term efficacy of adjuvant and neoadjuvant chemotherapy in patients with UTUCC.

7. Follow-up

   Patients should be examined every 3 months for at least a year with a history, physical examination, cystoscopy, urinalysis, and cytology. If nephron-sparing surgery is undertaken, close endoscopic surveillance is required because up to 75% of early recurrences can be missed with imaging alone. Because synchronous or metachronous bilateral disease can be seen in up to 4% of patients, regular urothelial imaging (IVP, CTU, or retrograde pyelogram) is required at least yearly. Depending on stage, grade, and presence of recurrence, follow-up intervals for UTUCC can be increased in a similar fashion to UCB surveillance to every 6 months for years 2 and 3, then yearly after. Chest radiographs and abdominopelvic cross-sectional imaging are initially obtained every 6 months and then yearly.

## Testicular Tumors

### GENERAL COMMENTS

Approximately 95% of testis tumors are derived from germ cells, whereas the rest arise from stromal cells. Germ cell tumors (GCTs) of the testis are broadly classified as seminoma or as nonseminoma because of differences in tumor biology and treatment paradigms. **Seminomas are exquisitely sensitive to radiation therapy, whereas both seminoma and nonseminomatous germ cell tumors (NSGCT) respond well to platinum-based combination chemotherapy.** Retroperitoneal lymphadenectomy continues to play an important role in the treatment of NSGCT in both the pre- and postchemotherapy settings and for seminoma in the postchemotherapy setting. Furthermore, the tumor markers beta-human chorionic gonadotropin (beta-HCG) and alpha-fetoprotein (AFP) play an essential role in diagnosis, staging, and treatment planning.

## INCIDENCE

In 2013 there will be an estimated 7,920 new cases of testis cancer with only 370 deaths attributed to the disease, largely owing to the effectiveness of multimodality therapy.

## ETIOLOGY

No definitive cause of testis cancer has been identified, but several risk factors are well established. Cryptorchidism is associated with a four- to sixfold increased risk of developing the disease. While the preponderance of risk is in the undescended testis, a slightly increased risk of testicular cancer is in the contralateral descended testis. It has been hypothesized that testicular dysgenesis might play a role in the development of testicular cancer, which may explain the link between male factor infertility and increased testicular cancer risk.

Men with a first-degree relative with testicular cancer also have increased risk for the disease. Furthermore, men with a personal history of testicular cancer are at an increased risk for tumor development in the contralateral testis. While the development of a metachronous testis is uncommon, close surveillance by monthly self-examinations is strongly advocated.

## EPIDEMIOLOGY

**Testicular cancer is most frequently observed in young men and is the most common solid tumor in men between the ages of 15 and 40.** Smaller peak incidences exist for men older than 60 years. The incidence of testis cancer is five times higher in white Americans than black Americans. Additionally, there exists considerable geographic variation in the incidence of testis cancer, with the highest rates observed in Scandinavian countries.

## NATURAL HISTORY

Germ cell tumors typically arise from areas of intratubular germ cell neoplasia (ITGCN), the testis cancer equivalent of CIS. From these lesions, GCTs may invade beyond the basement membrane to eventually replace some or all of the testicular parenchyma. Epididymal and spermatic cord involvement rarely occurs because tumor growth is contained by the tunica albuginea. **Approximately 50% of patients with ITGCN will progress to an invasive GCT within 5 years, and between 5% and 9% of**

**patients with GCT will have ITGCN in the contralateral testis. Contralateral testis biopsy is no longer advocated; however, the finding of contralateral ITGCN should merit aggressive surveillance or consideration of treatment**. The finding of microlithiasis on ultrasound may be associated with the presence of ITGCN; however, less than 2% with microlithiasis will develop testis cancer.

All GCTs identified in adults should be treated as malignant neoplasms. Metastatic dissemination most often occurs via the lymphatic route, typically first to the retroperitoneum. Several decades ago, the long-term survival rate for advanced testicular cancer was less than 10%, but now it is greater than 90% after the introduction of combination platinum-based chemotherapy. The majority of patients who die from testicular cancer do so within 3 years of diagnosis.

## PATHOLOGY

1. Germ cell neoplasms
   a. Seminoma
      1) Classic seminoma: **Classic seminoma accounts for approximately 85% of identified seminomas and 30% of all testicular GCTs**. Mixed tumors that contain any NSGCT components should be classified as NSGCT regardless of the proportion of seminoma. **Approximately 15% will also contain syncytiotrophoblastic elements, which may produce HCG. Thus the finding of an elevated HCG does not preclude the diagnosis of pure seminoma**. Conversely, AFP should never be elevated in a pure seminoma, and therefore, regardless of orchiectomy pathology, an elevated AFP should prompt the treating physician to consider the patient to have NSGCT. Peak incidence for seminoma is seen in the fourth and fifth decades of life, one decade later than NSGCT. Grossly, seminomas appear as well-defined, yellow-tan tumors.
      2) Spermatocytic seminoma: Typically seen in older patients (50% are older than 50 years), spermatocytic seminomas account for less than 1% of all testicular tumors. These lesions are not thought to arise from ITGCN. These tumors carry a favorable prognosis with little to no propensity for metastatic dissemination.

3) Anaplastic seminoma: This is **no longer considered a distinct subtype of seminoma**. While these tumors typically present at a later stage than classic seminoma, when adjusted for stage this pathologic subtype does not carry any prognostic importance.

b. Embryonal carcinoma

This represents approximately 3% of pure GCTs but may be a component of up to 25% of mixed GCTs. Embryonal carcinoma is the most undifferentiated NSGCT cell type and is considered an aggressive tumor type that is associated with a high rate of disease progression and metastasis. The proportion of embryonal carcinoma is generally considered to associate with a higher risk of occult metastatic disease in patients with clinical stage I NSGCT.

c. Teratoma

These tumors may be composed of endodermal, mesodermal, or ectodermal elements. It is the second most common testis tumor in children after yolk sac tumor. Teratoma may be classified as mature or immature depending on the degree of differentiation. Teratoma is not responsive to either radiotherapy or chemotherapy, and therefore metastatic deposits can only be cured with surgery. Many arise from transformation of NSGCT after chemotherapy. Teratoma may undergo malignant transformation to develop into a teratocarcinoma or grow to result in deleterious local effects, the latter described as *growing teratoma syndrome*.

d. Choriocarcinoma

This typically represents less than 1% of all NSGCT. It usually presents with metastatic disease and very high serum levels of HCG. **Choriocarcinoma has the propensity to metastasize hematogenously, and, as such, lung and brain metastases are common.** Because of tumor vascularity, brain metastasis is associated with a 4% to 10% risk of intracranial hemorrhage during chemotherapy.

e. Yolk sac tumor

It is the most common NSGCT in children. It is a rare tumor type in its pure form but may be present in up to 25% of mixed GCTs. Nearly all yolk sac tumors produce AFP, but not HCG. Approximately 50% of yolk sac tumors have the pathognomonic finding of Schiller-Duval bodies on microscopy.

2. Nongerm cell neoplasms
   a. Specialized gonadal stromal tumors
      1) Leydig cell tumor: This constitutes 1% to 3% of all testis tumors; it may present with gynecomastia because of the aromatization of excess androgens produced by the tumor. Approximately 10% of adult Leydig cell tumors are malignant; however, these tumors never are considered malignant in prepubertal patients. Histologic determination of malignancy is unreliable; therefore malignancy is often only identified by the presence of metastases.
      2) Sertoli cell tumor: This is less than 1% of testis tumors, and 10% are malignant. As with Leydig cell tumors, histology is unreliable, and malignancy is identified by the presence of metastases.
      3) Gonadoblastoma: This is associated with a dysgenetic gonads and patients suffering from disorders of sex development. Bilateral orchiectomy is indicated because 50% of such gonads will develop into malignant GCTs.

## STAGING

Unique to testis cancer, the AJCC staging system includes a separate category for tumor marker status to aid in identifying patients with high risk for relapse (Table 17-5). Fortunately, the vast majority of men with newly diagnosed testis cancer enjoy favorable 5-year survival. Indeed, the 5-year survival rate for patients with clinically localized disease is 99%, for patients with nodal metastases is 96%, and for patients with distant metastatic disease is 72%.

TABLE 17-5 **AJCC 7th Edition Staging System for Testicular Cancer**

***Primary Tumor (T)****

The extent of primary tumor is usually classified after radical orchiectomy, and for this reason a pathologic stage is assigned.

pTX - Primary tumor cannot be assessed

pT0 - No evidence of primary tumor (e.g., histologic scar in testis)

pTis - Intratubular germ cell neoplasia (CIS)

pT1 - Tumor limited to the testis and epididymis without vascular or lymphatic invasion; tumor may invade the tunica albuginea but not the tunica vaginalis

*(Continued)*

TABLE 17-5 **AJCC 7th Edition Staging System for Testicular Cancer—Cont'd**

pT2 - Tumor limited to the testis and epididymis with vascular or lymphatic invasion; tumor extending through the tunica albuginea with involvement of the tunica vaginalis

pT3 - Tumor invades the spermatic cord with or without vascular and lymphatic invasion

pT4 - Tumor invading the scrotum with or without vascular and lymphatic invasion

***Regional Lymph Nodes (N)***

*Clinical*

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph node metastasis

N1 - Metastasis with a lymph node mass 2 cm or less in greatest dimension; multiple lymph nodes, none >2 cm in greatest dimension

N2 - Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension; or multiple lymph nodes, any one mass >2 cm but not >5 cm in greatest dimension

N3 - Metastasis with a lymph node mass >5 cm in greatest dimension

***Distant Metastasis (M)***

M0 - No distant metastasis

M1 - Distant metastasis

M1a - Nonregional nodal or pulmonary metastasis

M1b - Distant metastasis other than to nonregional lymph node and lungs

***Serum Tumor Markers (S)***

SX - Marker studies not available or not performed

S0 - Markers within normal limits

S1 - LDH <1.5 x N** AND HCG (mIU/mL)
<5000 AND AFP <1000 (ng/mL) < 1000

S2 - LDH 1.5–10 x N OR HCG (mIU/mL)
5000-50,000 OR AFP (ng/mL)
1000-10,000

S3 - LDH >10 x N OR HCG (mIU/mL) >50,000 OR AFP (ng/mL) >10,000

*Note: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

**N indicates the upper limit of normal for the LDH assay.

*CIS*, Carcinoma in situ; *LDH*, lactate dehydrogenase; *HCG*, human chorionic gonadotropin; *AFP*, alpha fetoprotein.

*(From Edge SB, Byrd DR. Compton CC, et al, editors:* AJCC cancer staging manual*, ed 7, New York, 2010, Springer.)*

## CLINICAL PRESENTATION

The most common presenting symptom is a painless testicular mass. A 4- to 6-month delay in presentation is not uncommon; however, treatment delay is associated with more advanced disease and worse outcomes. **Approximately 10% to 20% of patients will present with symptoms of metastatic disease, such as cough, abdominal or supraclavicular mass, back pain, and lymphadenopathy**. Certainly, any young male presenting with a retroperitoneal mass should undergo thorough evaluation of the scrotal contents. Gynecomastia may be present in up to 2% of men secondary to elevation of HCG or the effect of tumor estradiol synthesis with Leydig cell tumors.

## DIAGNOSIS AND STAGING

1. Transcrotal ultrasound can confirm the presence of an intraparenchymal testicular mass, rule out benign processes such as a hydrocele or epididymitis, and effectively evaluate the contralateral gonad. The incidence of bilateral GCT is approximately 2% with the majority of bilateral tumors arising in a metachronous fashion.
2. Radical inguinal orchiectomy: Treatment of the primary tumor requires early clamping of the spermatic cord near the internal ring and complete removal of the testis. **While partial orchiectomy may be considered in select cases, the standard of care remains radical inguinal orchiectomy**. Scrotal orchiectomy or percutaneous biopsy should never be performed because of the theoretical risk of alteration to the lymphatic drainage of the testis resulting in inguinal metastases.
3. **Staging imaging involves a PA and lateral CXR and CT scan of the abdomen and pelvis with contrast**. In the absence of lymphadenopathy on CT of the abdomen and pelvis, a CT scan of the chest is generally not preferred. Additionally, brain MRI and nuclear medicine bone scan should be considered if clinically indicated. Lastly, sperm banking should be discussed with patients before undergoing chemotherapy or radiation therapy.
4. Tumor markers
    a. Over all stages, 90% of patients with nonseminomatous tumors will have an elevation of HCG and/or AFP. After therapy, tumor markers should display a logarithmic pattern

of decrease in accordance with their half-lives. Sustained elevation of markers or slow decreases after orchiectomy or RPLND suggests residual disease; however, normalization of markers is not definite evidence of complete surgical cure.

b. HCG: This is a heterodimeric protein with immunologically distinct chains. Circulating levels are extremely low (1 ng/mL) in normal males. The syncytiotrophoblastic tissue of some GCTs produces HCG. It can therefore be detected in almost all choriocarcinomas, 40% to 60% of embryonal cell carcinomas, and 5% to 10% of pure seminomas. The half-life for HCG is roughly 24 hours. Because beta-HCG shares structural homology with luteinizing hormone (LH), spurious elevations may occur in patients with hypogonadism secondary to gonadal failure.

c. AFP: This is an oncofetal protein detected in testis and liver tumors. It is produced by yolk sac elements that may or may not be histologically recognized. This substance is *not* produced in pure choriocarcinoma or pure seminoma. The presence of elevated AFP in a patient with histologic seminoma precludes the diagnosis of pure seminoma. The half-life of AFP is 5 to 7 days.

d. LDH: This general cellular enzyme is not specific for testicular lesions but is thought to correlate with tumor burden. It may play some role in monitoring patients with advanced seminoma and in marker negative patients with NSGCT and persistent disease.

## TREATMENT AFTER ORCHIECTOMY

1. Seminoma
   a. Clinical stage I: Approximately 80% of patients diagnosed with seminoma will have clinical stage I disease. Seminomas are sensitive to both radiation and platinum-based chemotherapy. **Accepted treatment options for clinical stage I include surveillance, primary radiotherapy, and primary chemotherapy with single agent carboplatin.** Fortunately, the long-term cancer control is nearly 100% with any of these modalities. **The decision whether to pursue surveillance or active treatment rests in the presence or absence of risk factors for disease progression, the individual patient's preferences, and the morbidity associated with each**

**therapeutic strategy.** Risk factors for disease progression in seminoma include tumor size greater than 4 cm and rete testis invasion. Patients with zero, one, or both risk factors have a 5-year relapse risk of 12%, 16%, and 32%, respectively.

1) Surveillance: This involves careful monitoring with initiation of treatment at the first sign of disease progression. Monitoring includes frequent tumor markers, chest radiographs, and abdominopelvic CT scans at prespecified intervals, which grow longer with increasing time since diagnosis. Given the fact that relapse-free survival for all patients with clinical stage I seminoma is approximately 80%, surveillance prevents overtreatment, and thus the morbidity of either chemotherapy or radiotherapy, in 8 out of 10 men. Additionally, cancer-specific survival after salvage therapy approaches 100%, lending further support to surveillance. Treatment at the time of relapse is dictated by the stage at relapse and requires chemotherapy, radiotherapy, or both. Surveillance for clinical stage I seminoma is limited by the need for long-term observation given that relapse after 5 years is not uncommon. There is some concern over the long-term consequences of multiple CT scans required for surveillance. Unlike NSGCTs, serum tumor markers have limited utility with detecting recurrence in seminoma.
2) Primary radiotherapy: This generally involves delivery of approximately 25 Gy in a "dog leg" pattern to the retroperitoneum and ipsilateral pelvis. Recurrence within the radiation field occurs in less than 1% of the cases, thereby obviating the need for frequent abdominopelvic CT scans after radiotherapy. Side effects include acute toxicity of treatment (nausea, vomiting, hematologic), oligospermia, and hematologic abnormalities. The incidence of secondary malignancy has been estimated to be as high as 18% within 25 years of radiation.
3) Primary chemotherapy: Primary chemotherapy involves one or two cycles of single-agent carboplatin as an alternative to radiation. This approach is associated with a 5-year relapse-free survival over 90% with less late toxicity compared to radiation. Because relapse usually

occurs within the retroperitoneum, abdominopelvic CT scan cannot be excluded in follow-up surveillance as it can be for primary radiation.

a) Clinical stage IIA and IIB: From 10% to 15% of patients with seminoma will have CSIIA-B. Standard treatment at most centers is "dog leg" radiation with 25 to 35 Gy.

b) Clinical stage IIC and III: See below.

c) Postchemotherapy residual mass: See below.

2. Nonseminomatous germ cell tumors
   a. Clinical stage I: As in clinical stage I seminoma, numerous therapeutic options exist for men with clinical stage I NSGCT, including surveillance, primary retroperitoneal lymph node dissection (RPLND), and primary chemotherapy. Again, long-term survival is nearly 100% for RPLND, primary chemotherapy, and surveillance, so treatment decision making must be individualized to optimize patient satisfaction. For 70% to 80% of patients, orchiectomy alone will be curative. To avoid overtreatment, a risk-adapted approach is used at most centers. Risk factors for occult metastasis include the presence of lymphovascular invasion in the orchiectomy specimen and predominance of embryonal carcinoma (usually greater than 40% to 45%) in the orchiectomy specimen.
      1) Surveillance: Given the high cure rate with orchiectomy alone and excellent salvage rate in relapsed patients, surveillance is a reasonable option for most patients, particularly those without risk factors for occult metastasis. As in any disease requiring long-term observation, one disadvantage of surveillance is the need for long-term cross-sectional imaging, with the associated risk of secondary neoplasia. The use of MRI technology has reduced this risk, although multiple factors contribute to the ability to use serial MRI, including familiarity of the operating radiologist. High rates of noncompliance with surveillance protocols have been reported, and certainly the ability of each patient to commit to observation should be evaluated prior to undertaking surveillance.
      2) RPLND: This provides effective control of the most common site of metastasis, the retroperitoneum. The incidence

of teratoma is 15% to 25% for those with occult metastasis. Only RPLND can treat teratoma because it is resistant to both chemotherapy and radiation. Different RPLND templates have been proposed based on lymphatic drainage of the involved testis. Controversy exists over the use of unilateral templates. Only the full bilateral template is associated with a low enough retroperitoneal recurrence rate (less than 2%) that abdominopelvic CT scan can be eliminated in follow-up surveillance. Nerve-sparing techniques can reduce but not eliminate the risk of retrograde ejaculation. RPLND can be technically challenging and is best reserved for high-volume centers.

3) Primary chemotherapy: Two cycles of bleomycin, etoposide, and cisplatin (BEP) offer the greatest chance of relapse-free survival; however, long-term surveillance with abdominopelvic CT is still required to monitor for retroperitoneal recurrence. While the presence of teratoma on the orchiectomy specimen has been associated with its presence in the retroperitoneum, the absence of teratoma on the orchiectomy specimen does not rule out the presence of retroperitoneal teratoma. As previously mentioned, teratoma is resistant to chemotherapy and remains subject to surgical control. It is important to recognize the risk of late cardiovascular toxicity and secondary malignancy with chemotherapy; however, the incremental risk associated with two cycles of BEP remains largely unknown.

b. Clinical stage IS: The presence of elevated serum tumor markers after orchiectomy without clinical evidence of metastatic disease are treated as clinical stage IIC-III (see below).

c. Clinical Stage IIA and IIB: Both RPLND and induction chemotherapy (EPx4, BEPx3) offer excellent overall survival rates to patients with radiographically evident nodal disease. Induction chemotherapy is generally preferred in patients with elevated tumor markers or in the presence of bulky lymphadenopathy (greater than 3 cm), and RPLND is preferred as initial therapy for those at high risk of harboring teratoma but low risk for systemic disease. For patients who do not fall into either of these groups, the decision between RPLND and induction chemotherapy is controversial and in all cases should be tailored to individual patient preferences.

    1) Benefits of primary RPLND include that it allows the 15% to 35% of patients with pathologically negative lymph nodes to avoid unnecessary chemotherapy and it eliminates the need for future therapy in approximately 30% of patients with teratoma. The disadvantage of primary RPLND largely surrounds surgical morbidity, in particular, a considerable risk of ejaculatory dysfunction (10% to 20%).
    2) Induction chemotherapy with BEPx3 or EPx4 results in a complete response for 60% to 80% of patients. Furthermore, chemotherapy regimens are relatively well established, and, compared with RPLND, have potentially less variation with regard to treatment quality. The disadvantage of induction chemotherapy remains the late toxicity associated with chemotherapy and, if relapse occurs, the possibility of establishing chemo resistance.

3. Postchemotherapy residual mass:
    a. Seminoma: **Residual masses are present on 60% to 80% of abdominopelvic CT scans in seminoma patients after first-line chemotherapy; however, the majority of these masses will spontaneously involute within 18 months.** The use of RPLND in the treatment of postchemotherapy residual disease remains controversial. There is a significant desmoplastic reaction within the retroperitoneum from chemotherapy rendering postchemotherapy RPLND for seminoma technically challenging. Furthermore, unlike NSGCT, there is less concern for teratoma and malignant transformation with seminoma. For masses smaller than 3 cm in size, the risk of viable tumor is less than 5%. Recently, fluorodeoxyglucose positron emission tomography (FDG-PET) has demonstrated the ability to identify which seminoma patients with a residual mass have a viable tumor. Therefore, observation can be safely employed for seminoma patients with residual masses less than 3 cm and for masses greater than 3 cm that are PET negative.
    b. NSGCT: Management of the post-chemotherapy mass in patients with NSGCT is considerably different than for patients with seminoma. **The distribution of histologies in residual NSGCT masses is as follows: 40% necrosis, 45% teratoma,**

**and 15% viable malignancy.** Therefore, at our institution, patients with a postchemotherapy mass greater than 1 cm will undergo a postchemotherapy RPLND. Unlike in seminoma where the risk of teratoma is quite low, the significant risk of teratoma renders FDG-PET unreliable given the fact that teratoma is not PET-avid. Thus, FDG-PET is not recommended for use in patients with NSGCT. **Complete resection of the residual mass is paramount, and bilateral RPLND should be performed with the use of nerve-sparing techniques wherever possible.**

4. Advanced testicular cancer

Clinical stage IIC and III seminoma and NSGCT are treated similarly with induction chemotherapy, according to the International Germ Cell Consensus Classification risk (Table 17-6). Chemotherapy regimens are platinum based with cisplatin being superior to carboplatin in randomized

TABLE 17-6 **International Germ Cell Consensus Risk Classification for Metastatic Germ Cell Tumor**

| Prognosis | Seminoma | NSGCT |
|---|---|---|
| Good | Any primary;<br>without nonpulmonary visceral metastasis;<br>normal AFP, any HCG or LDH | Testis/retroperitoneal primary;<br>without nonpulmonary visceral metastasis<br>with good tumor markers:<br>AFP <1000 ng/mL, HCG <5000 mIU/mL, LDH <1.5x upper limit normal |
| Intermediate | Any primary;<br>nonpulmonary visceral metastasis present;<br>normal AFP, any HCG or LDH | Testis/retroperitoneal primary;<br>without nonpulmonary visceral metastasis;<br>with intermediate markers:<br>AFP 1000–10,000 ng/mL, or hCG 5000–50,000 mIU/mL, or LDH 1.5–10x upper limit normal |
| Poor | No patients with seminoma are classified as poor risk | Mediastinal primary; or<br>nonpulmonary visceral metastasis present; or<br>poor tumor markers:<br>AFP > 10,000 ng/mL, or HCG > 50,000 mIU/mL, or LDH >10x upper limit normal |

trials for advanced testicular cancer. Attempts have been made to avoid bleomycin in low-risk patients because of the pulmonary toxicity.

   a. Seminoma: Ninety percent of advanced seminoma is classified as good risk and can be treated with BEPx3 or EPx4 for a 5-year overall survival of 91%. The 10% of advanced seminoma with nonpulmonary metastasis is classified as intermediate risk and treated with BEPx4 for a 5-year overall survival of 79%. Poor prognosis tumors do not exist for seminoma.
   b. NSGCT: For good-risk patients, BEPx3 or EPx4 has a 5-year overall survival of greater than 90%. BEPx4 is the standard for intermediate risk and poor risk with 5-year overall survival rates of 79% and 48%, respectively. Etoposide-ifosfamide-cisplatin (VIP) x 4 has been also been used for intermediate- and poor-risk NSGCT; however, it is limited by increased hematologic and genitourinary toxicity.

5. Patient surveillance

   For detailed guidelines concerning various surveillance protocols, see the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (www.nccn.org).

# Penile Cancer

## GENERAL CONSIDERATIONS

Penile carcinoma remains an uncommon diagnosis in the United States, representing only 0.5% of all malignancies. Nonetheless, the disease accounts for up to 10% of all male cancers in the developing world. In the United States, there is an estimated 1,570 cases of penile cancer in 2013 with approximately 310 deaths from the disease. Because of its rarity, little high-quality evidence exists upon which to base clinical practice.

## PENILE CANCER

1. Premalignant lesions
   a. Condylomata acuminata (genital warts): These lesions are caused by human papillomavirus (HPV) infection and may involve the glans, prepuce, or shaft of the penis. They are generally considered benign papillomatous growths;

however, HPV virus types 16, 18, 31, 33, 35, and 39 are associated with anogenital cancers. Several topical treatment options are available for condylomata, including podophyllotoxin 0.5% and imiquimod 5% cream. Patients who desire immediate wart removal or those with refractory lesions are candidates for cryoablation, local excision, or laser ablation. Prevention should be reinforced in all patients with condyloma because of the high risk of transmission through sexual contact and the etiologic association of HPV infection with cervical cancer in women. The HPV quadrivalent vaccine was found to be safe in males and females between the ages of 9 and 26 years. It is recommended for the prevention of condylomata acuminate in both genders. The incidence of cervical cancer is expected to decrease over time with the widespread utilization of the HPV vaccine. A decrease in the incidence of other HPV-associated anogenital cancers, including penile cancer, is also expected; however, further study will be required to document these epidemiologic phenomena.

b. Buschke-Löwenstein tumor: This lesion is also known as *giant condyloma acuminatum* and *verrucous carcinoma*. These tumors do not harbor very low metastatic potential but may grow to cause local destruction and symptoms. It may be treated with penile sparing surgery, but total or partial penectomy may be considered. Due to the high predilection for recurrence, patients with giant condylomata must be carefully monitored.
c. Leukoplakia: This term describes a white cutaneous plaque that may be hypertrophic or atrophic. It typically results from chronic irritation. Leukoplakia is considered a premalignant condition to the development of squamous cell carcinoma. Ten percent to 20% of lesions show evidence of dysplasia. Circumcision and surgical excision are the preferred treatments, but radiation therapy has also been used.
d. Balanitis xerotica obliterans (BXO): This subcategory of lichen sclerosus atrophicus limited to the male genitalia is associated with destructive inflammation, phimosis, urethral stricture, meatal stenosis, and penile squamous cell carcinoma. These hypopigmented, papular, or atrophic lesions typically involve the glans penis and urethral meatus.

Initial management should include biopsy to exclude the presence of carcinoma, followed by topical steroids. There is a 3% to 9% risk of development of penile carcinoma in lichen sclerosus. Long term follow-up and self-examination are recommended, with low threshold for biopsy of any suspicious lesions.

e. Bowenoid papulosis: This is an uncommon genital dysplasia thought to be caused by HPV type 16. Although histology of this lesion resembles squamous cell CIS, the course of Bowenoid papulosis is universally benign. Unlike Bowen disease, it never progresses to an invasive carcinoma. Given the benign course of this disease, less morbid strategies such as excision, cryoablation, topical 5-fluorouracil, or laser photocoagulation should be considered.

2. CIS

If involving the glans or prepuce, CIS is also known as erythroplasia of Queyrat, whereas CIS of the penile shaft is generally referred to as Bowen disease. These lesions appear as localized, velvety red patches but may develop into painful ulcers. Bowen disease may appear scaly and is no longer thought to be associated with internal malignancies. Lesions on the prepuce can be safely treated with circumcision. Although the standard management of CIS remains local excision with a 5-mm margin, other alternatives include laser ablation, topical 5-fluorouracil, and imiquimod cream. These alternatives achieve acceptable local control with organ preservation. It is essential to perform a deep biopsy to rule out invasive carcinoma.

3. Invasive squamous cell carcinoma

a. Etiology

**The development of penile carcinoma has long been associated with poor hygiene and exposure to irritants, carcinogens, or possible viral pathogens. Neonatal circumcision has been shown to be protective against the development of penile cancer; however, adult circumcision fails to provide the same risk reduction.** Infection with HPV 16 or HPV 18 is also thought to be a risk factor for penile cancer and is associated with 30% to 60% of penile carcinomas. Lichen sclerosis, tobacco usage, and genital ultraviolet radiation are also associated with penile carcinoma development.

b. Natural history

Carcinoma of the penis usually begins as a small lesion on the glans or prepuce, which may be exophytic or ulcerative. Invasion is usually direct and capable of destroying surrounding tissue. Metastases from penile cancer travel via the lymphatics in an invariable pattern; first to superficial inguinal lymph nodes, then deep inguinal nodes, followed by extension into the pelvis. The right and left lymphatic drainage systems are interconnected, so metastatic deposits may travel to the contralateral lymphatic landing zones. Distant metastases typically occur late in the disease after inguinal lymph nodes become clinically evident. The most common sites of distant metastasis include the bone, liver, and lung. Death is usually secondary to involvement of regional nodes, which results in skin necrosis, chronic infection, sepsis, or hemorrhage secondary to erosion into the femoral vessels.

c. Clinical features

The primary penile lesion may assume the appearance of a nodule, wartlike growth, ulceration, or vesicle. The primary lesion develops on the glans, prepuce, corona, or penile shaft in approximately 48%, 21%, 6%, and less than 2% of cases, respectively. Phimosis is present in as many as 50% of patients, and its presence may prevent identification of the lesion until it is larger in size. Between 15% and 50% of patients with carcinoma of the penis have a delay in presentation of over 1 year. Lymph nodes are palpably enlarged in almost 50% of patients.

d. Diagnosis and staging

**Diagnosis depends on an adequate tissue biopsy or tumor excision. The tumor should be assessed for depth of invasion, lymphovascular invasion, perineural invasion, and histologic grade.** Penile carcinoma is broadly classified into high grade and low grade by Broders classification. These histologic features of the biopsy have important prognostic significance and help determine the need for subsequent inguinal lymph node management.

Preoperative staging of penile cancer can be challenging. Tumor size, location, fixation, and involvement of the corporal bodies should be assessed by physical examination. Contrast enhanced penile MRI may be a useful adjuvant to detect corporal invasion for patients being considered for penile-sparing procedures. **Careful bilateral palpation of the inguinal**

**regions is of extreme importance. Unfortunately, groin CT and MRI imaging provide little useful information over physical examination, but can be considered for patients with prior inguinal surgery or obese patients.** Staging for penile carcinoma most commonly uses the unified Union Internationale Contre le Cancer (UICC) and American Joint Commission on

TABLE 17-7 **AJCC 7th Edition Staging System for Penile Cancer**

***Primary Tumor (T)***

TX - Primary tumor cannot be assessed
T0 - No evidence of primary tumor
Tis – Carcinoma in situ
Ta – Noninvasive verrucous carcinoma*
T1a - Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3-4)
T1b - Tumor invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated
T2 - Tumor invades corpus spongiosum or cavernosum
T3 – Tumor invades urethra
T4 – Tumor invades other adjacent structures

***Regional lymph nodes (N)***

*Clinical stage definition**
cNX - Regional lymph nodes cannot be assessed
cN0 - No palpable or visibly enlarged inguinal lymph nodes
cN1 – Palpable mobile unilateral inguinal lymph node
cN2 – Palpable mobile multiple or bilateral inguinal lymph nodes
cN3 – Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
*Pathologic stage definition*
pNX - Regional lymph nodes cannot be assessed
pN0 – No regional lymph node metastases
pN1 – Metastasis in a single inguinal node
pN2 – Metastasis in multiple or bilateral inguinal nodes
pN3 – Extranodal extension of lymph node metastasis or pelvic lymph node unilateral or bilateral

***Distant metastasis (M)***

M0 - No distant metastasis
M1 – Distant metastasis

*Note: Lymph node metastasis outside of the true pelvis in addition to the visceral or bone sites

*(From Edge SB, Byrd DR. Compton CC, et al, editors:* AJCC cancer staging manual, *ed 7, New York, 2010, Springer.)*

Cancer (AJCC) staging system (Table 17-7). Similar to other malignancies, 5-year survival is largely contingent upon stage at presentation. Patients with disease localized to the penis demonstrate 5-year survival rates of 80% to 90%, whereas patients with nodal disease and distant metastatic disease have 5-year survival rates of 50% to 60% and 5% to 15%, respectively.

4. Treatment
   a. Primary lesion

   Suspicious penile lesions should undergo biopsy with a deep margin to ensure satisfactory staging. Penile tumors that are stage Tis, Ta, or low-grade T1 may be eligible for penile-sparing techniques. The goal is to maintain penile length, function, and aesthetics without compromising survival. Although acceptable oncologic outcomes can be achieved with this approach, these patients are at greater risk of local recurrence and must have close long-term follow-up. It is important to recognize that patient compliance and reliability with long-term follow-up may be a limitation to penile-sparing techniques.

   1) **Limited surgical excision:** Although historically a 2-cm tumor margin was thought necessary, this recently has been challenged. Several series have shown no determent to oncologic outcomes with a margin as close as 5 mm, although a 10 mm margin is more commonly reported in series. Intraoperative frozen sections should be performed to ensure microscopically negative margins. Limited excision of glans or shaft lesions can be performed with or without the use of grafts or flaps for reconstruction. Lesions confined to the prepuce may be treated by circumcision only with satisfactory oncologic outcome.
   2) **Laser ablation:** The four most widely used laser energy sources include the $CO_2$, argon, Nd:YAG, and potassium titanyl phosphate (KTP) lasers. The superficial depth of penetration of the $CO_2$ laser (limited to 0.1 mm) makes it suboptimal for treatment of penile carcinoma, with recurrence rates as high as 50%. Conversely, the Nd:YAG laser results in protein denaturation at a depth of up to 6 mm by emitting at a wavelength of 1060 nm. Although overall recurrence rates after laser ablation have been reported around 8% for penile Tis and 10% to 25% for T1 lesions, results from more contemporary

series using the Nd:YAG laser with tumor base biopsies have been more encouraging, with recurrence rates below 7%. Close surveillance and patient self-examination are paramount after laser ablation. Recurrences are best treated with wide local excision or partial amputation.

3) **Mohs microsurgery:** This involves a layer-by-layer complete excision of the penile lesion in multiple sessions using a fixed tissue technique that theoretically offers improved precision and control of the negative margin while maximizing organ preservation. Although results with Mohs microsurgery are likely equivalent to those of limited surgical excision with intraoperative frozen section for CIS or for small superficially invasive tumors, the use of this technique in higher stage tumors (corpora cavernosum or urethral involvement) or in those larger than 3 cm is discouraged.
4) **Radiation:** Both external beam radiation (EBRT) and brachytherapy are therapeutic options for patients with localized penile carcinoma. Often circumcision is necessary to allow the lesion to be exposed for irradiation. EBRT is limited by the need for penile immobilization but has less operator dependence than brachytherapy. Interstitial radiation has been used successfully to treat penile carcinoma with a variety of radioisotopes, including radium$^{226}$, iridium$^{192}$, and cesium$^{137}$. Data from a number of centers show that penile conservation may be achieved in up to 83% of patients, with 5-year local recurrence rates varying between 24% and 57%. The pathologic variables associated with treatment failure in most studies have been the presence of corporal invasion and tumor size greater than 4 cm. Although some series reported 5-year disease-free survival rates as high as 78%, delayed side effects have been reported in up to 53% of patients. The most common complications include urethral stricture disease (45%) and penile necrosis (23%). Indications for lymphadenopathy are the same as for surgery; however, only tumor biopsy information is available rather than pathologic stage from resection.
5) **Partial or total penectomy:** Large stage T1 tumors and T2 lesions of the glans or penile shaft should be treated

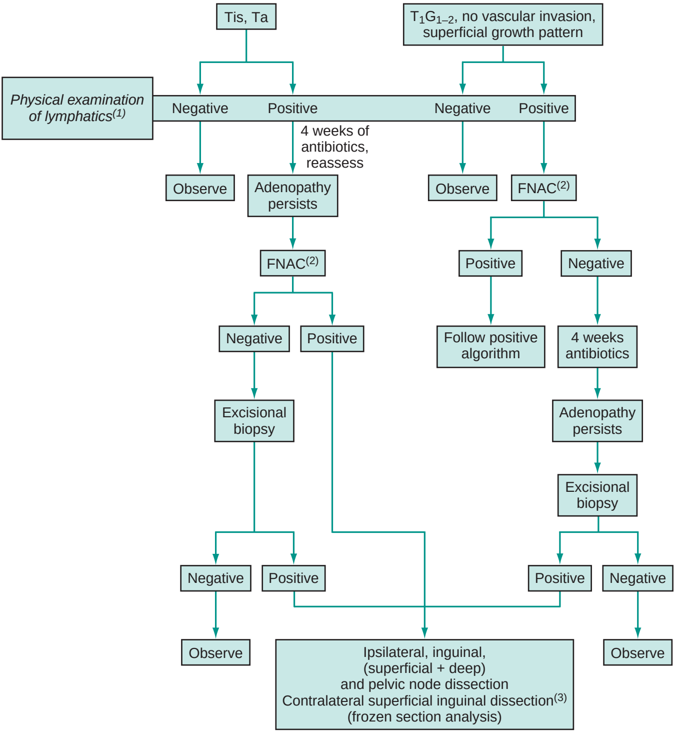
by partial penile amputation, ensuring at least a 1-cm tissue margin proximal to the tumor. Local wedge resection has a 50% recurrence rate compared to 8% or less with partial penectomy. In bulky T3 and T4 tumors or if the tumor location is such that amputation would leave a penile stump inadequate for voiding or sexual activity, a total penectomy with perineal urethrostomy is preferred.

b. Management of the inguinal lymph nodes

**For patients with invasive penile carcinoma, the most important prognostic factor is the presence and extent of inguinal lymph node metastases.** It is rational to perform a traditional inguinal lymphadenectomy in those patients with clinically positive lymph nodes, given the fact that patients with disease limited to the inguinal nodes can be cured with surgery alone and metastatic disease to the groin remains relatively resistant to chemotherapy and radiation. **Complications from lymphadenectomy remain considerable and include skin necrosis, wound infection, and debilitating lymphedema.** Advances in surgical technique and postoperative management have reduced the complication rate, but it remains substantial.

1) **Palpable inguinal adenopathy:** It is estimated that between 8% and 64% of patients with clinically palpable lymph nodes will harbor metastasis, whereas the remainder of patients suffer adenopathy from infection or inflammation. Historically all patients were given a 4- to 6-week treatment course of antibiotics, and if adenopathy remained, they underwent lymphadenectomy. This practice is no longer recommended because of concerns of delaying potentially curative intervention. Therefore **current recommendations are to perform a fine-needle aspiration of enlarged lymph nodes at the time of or soon after the treatment of the primary tumor**. The sensitivity and specificity of this technique is 93% and 91%, respectively. If cytology is negative but clinical concern is high, then an excisional biopsy should be performed.
2) **Nonpalpable lymph nodes:** Inguinal lymphadenectomy is associated with an almost 80% 5-year overall survival rate for patients with minimal lymph node involvement. **A risk-adapted approach should be undertaken**

**to identify the 20% to 25% of patients harboring occult metastasis** in clinically negative nodes, while avoiding overtreatment in the remaining 75% to 80% with truly negative nodes. Patients are divided into low- and high-risk strata based on pathologic features of the primary penile tumor. Patients with Tis and Ta tumors have a low risk of metastasis (less than 16%) and can be managed expectantly (Figure 17-1). Patients with corporal inva-


Tis, Ta
T₁G₁₋₂, no vascular invasion, superficial growth pattern
Physical examination of lymphatics(1)
Negative
Positive
Negative
Positive
4 weeks of antibiotics, reassess
Observe
Adenopathy persists
Observe
FNAC(2)
FNAC(2)
Positive
Negative
Negative
Positive
Follow positive algorithm
4 weeks antibiotics
Excisional biopsy
Adenopathy persists
Excisional biopsy
Negative
Positive
Positive
Negative
Observe
Ipsilateral, inguinal, (superficial + deep) and pelvic node dissection Contralateral superficial inguinal dissection(3) (frozen section analysis)
Observe

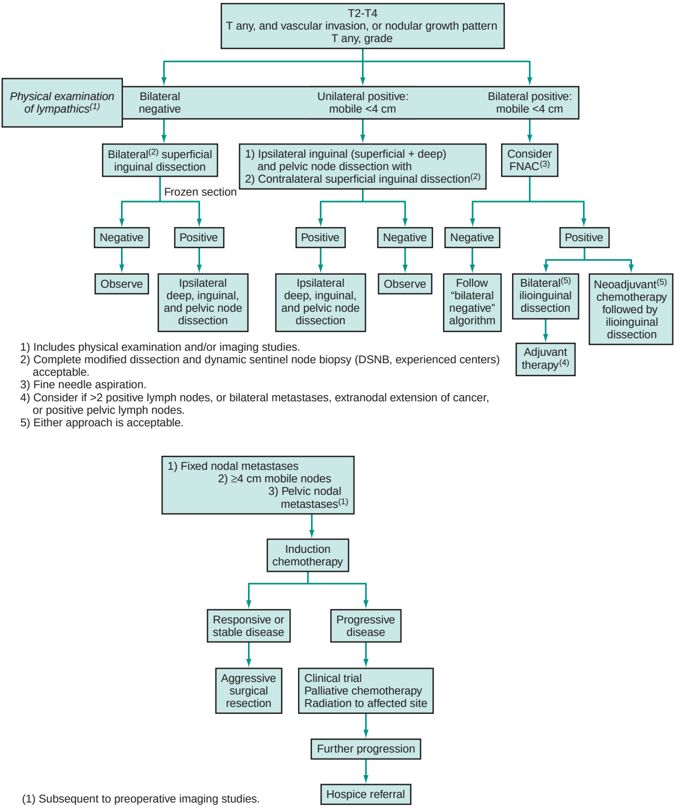
1) Includes physical examination and/or imaging studies.
2) Fine needle aspiration cytology.
3) Complete modified dissection and dynamic sentinel node biopsy (DSNB, experienced centers) acceptable.

**FIGURE 17-1 Management of the inguinal basins in low- and intermediate-risk patients.** (From Pettaway CA, Lance RS, Davis JW: Tumors of the penis. In Wein AJ, editor: *Campbell-Walsh urology,* ed 10, Philadelphia, 2011, Saunders Elsevier.)

sion (pT2) are at high risk for metastasis (greater than 64%). Patients with pT1 disease represent a heterogeneous cohort with heterogeneous outcomes. Pathologic features that should prompt lymphadenectomy in patients with pT1 penile carcinoma include high-grade histology, nodular growth pattern, or the presence of lymphovascular invasion. Patients with low-grade T1 disease with superficial growth patterns and no lymphovascular invasion should be considered as having an intermediate risk of metastasis. Patients in the risk group should be considered for prophylactic lymphadenectomy because they have a 50% to 70% risk of nodal metastasis (Figure 17-2). Patients who do not undergo a prophylactic lymphadenectomy should have very close and frequent follow-up in order to prompt immediate lymphadenectomy at the first indication of adenopathy.

3) **Lymphadenopathy extent: Patients with palpable lymph nodes should undergo a superficial and deep inguinal lymphadenectomy on the ipsilateral side. These patients should also undergo a contralateral superficial inguinal lymphadenectomy, even if nodes are nonpalpable, because contralateral inguinal node involvement may be present in 50% of patients**. Ipsilateral pelvic lymphadenectomy adds minimal morbidity and provides useful staging information in patients with positive lymph nodes. The margins of dissection of the inguinal lymphadenectomy include the inguinal ligament, the adductor longus, the sartorius, and the base of the femoral triangle. The fascia lata separates the superficial from the deep inguinal lymph node compartments. The sartorius muscle may be detached from the anterior superior iliac spine and rotated medially to cover the femoral vessels. Alternatively, gracilis or rectus abdominis flaps may be used to fill large defects after resecting large masses, thus preventing vessel erosion and skin necrosis.

Patients with clinically negative nodes but at high risk of metastasis by primary tumor characteristics may be considered for a more limited dissection with frozen sections. If any nodes return positive, then the surgeon should proceed to an ipsilateral superficial and deep


T2-T4
T any, and vascular invasion, or nodular growth pattern
T any, grade
Physical examination of lympathics(1)
Bilateral negative
Unilateral positive: mobile <4 cm
Bilateral positive: mobile <4 cm
Bilateral(2) superficial inguinal dissection
1) Ipsilateral inguinal (superficial + deep) and pelvic node dissection with
2) Contralateral superficial inguinal dissection(2)
Consider FNAC(3)
Frozen section
Negative
Positive
Observe
Ipsilateral deep, inguinal, and pelvic node dissection
Positive
Negative
Ipsilateral deep, inguinal, and pelvic node dissection
Observe
Negative
Positive
Follow "bilateral negative" algorithm
Bilateral(5) ilioinguinal dissection
Neoadjuvant(5) chemotherapy followed by ilioinguinal dissection
Adjuvant therapy(4)
1) Fixed nodal metastases
2) ≥4 cm mobile nodes
3) Pelvic nodal metastases(1)
Induction chemotherapy
Responsive or stable disease
Progressive disease
Aggressive surgical resection
Clinical trial
Palliative chemotherapy
Radiation to affected site
Further progression
Hospice referral

1) Includes physical examination and/or imaging studies.
2) Complete modified dissection and dynamic sentinel node biopsy (DSNB, experienced centers) acceptable.
3) Fine needle aspiration.
4) Consider if >2 positive lymph nodes, or bilateral metastases, extranodal extension of cancer, or positive pelvic lymph nodes.
5) Either approach is acceptable.

(1) Subsequent to preoperative imaging studies.

**FIGURE 17-2 Management of the inguinal basins in high-risk patients.** (From Pettaway CA, Lance RS, Davis JW: Tumors of the penis. In Wein AJ, editor: *Campbell-Walsh urology,* ed 10, Philadelphia, 2011, Saunders Elsevier.)

ilioinguinal lymphadenectomy and contralateral superficial inguinal lymphadenectomy. Sentinel lymph node biopsy with dye and/or radioactive tracer has an acceptable sensitivity in detecting occult metastasis in patients with nonpalpable lymph nodes but may be limited to experienced centers.

c. Advanced disease

Patients who present with bulky adenopathy and/or unresectable primary tumors should be considered for neoadjuvant chemotherapy followed by aggressive surgical resection. Similarly, patients with poor pathologic features after lymphadenectomy (extranodal extension, two or more positive nodes, bilateral inguinal metastases, or positive pelvic nodes) should be considered for systemic chemotherapy in the adjuvant setting. An optimal chemotherapy regimen for penile cancer has yet to be defined. Single-agent therapy with cisplatin, methotrexate, bleomycin, or cyclophosphamide and various combination therapies (bleomycin/vincristine/methotrexate, methotrexate/bleomycin/cisplatin, cisplatin/5-fluorouracil) have been tried with limited success. Up to 30% of patients will exhibit a partial response, but complete responses are rare. Chemotherapy with ifosfamide, paclitaxel, and cisplatin are effective in head and neck squamous cell carcinomas and have shown promising results in phase II trials with penile cancer patients.

5. Prognosis

The 5-year survival rate in patients without palpable adenopathy is 65% to 80%. Patients with pathologically negative inguinal nodes enjoy 5-year survival rates approaching 90%. Not surprisingly, increasing disease burden is associated with worse survival, with 5-year survival rates of 77% in patients with minimal nodal involvement compared to 20% to 50% in patients with a large burden of nodal disease.

6. Surveillance

Surveillance strategies should be tailored to the individual patient's risk of recurrence, varying by the pathologic characteristics of the primary tumor and the treatment employed. Men at a higher risk for locoregional recurrence that should have more rigorous follow-up include those treated with penile sparing techniques; patients with clinically negative inguinal lymph nodes who are managed without lymphadenectomy despite high-risk primary tumors (pT2-3, high grade T1, vascular invasion); and those with lymph node metastases after lymphadenectomy. Good candidates for less stringent surveillance include patients with low-risk primary tumors (pTis, pTa, and low grade pT1) and those with negative inguinal nodes after lymphadenectomy whose primary tumors were managed with partial or total penectomy.

## CLINICAL PEARLS

1. Treatment of small renal masses has evolved to favor the use of nephron-sparing approaches whenever technically feasible to optimize posttreatment renal function.
2. Despite challenges with adequate endoscopic sampling in patients with upper tract urothelial cell carcinoma (UTUCC), combining imaging findings with cytologic data provides the treating urologist with adequate information to formulate a treatment plan.
3. The optimal treatment approach for patients with clinical stage I nonseminomatous germ cell tumor (NSGCT) should take into account patient risk factors, preferences, attitude towards risk, and ability to adhere to strict surveillance.
4. Appropriate management of the primary tumor and inguinal lymph node basins is paramount in the treatment of patients with penile cancer.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What are the long-term benefits of nephron-sparing surgery?*
2. *For which patients with small renal masses is active surveillance most appropriate?*
3. *What is the risk of developing upper tract urothelial cell carcinoma (UTUCC) in a patient with a history of urothelial bladder cancer? What is the risk of subsequently developing bladder cancer in a patient diagnosed with UTUCC?*
4. *What is the importance of removing the bladder cuff at the time of radical nephroureterectomy?*
5. *How does the treatment paradigm differ in clinical stage I nonseminomatous germ cell tumors (NSGCTs) compare to clinical stage I seminomas?*
6. *A patient has mixed germ cell tumor (GCT) testis cancer with persistently elevated tumor markers after orchiectomy, despite no radiographic evidence of disease (clinical stage IS). How should this patient be treated?*
7. *Which HPV subtypes are associated with penile carcinoma? What percent of penile cancers are thought to be associated with HPV infection?*
8. *Which pathologic features of a penile tumor places a patient with nonpalpable lymph nodes at high risk for inguinal metastasis? How should they best be managed?*

## SUGGESTED READING

### *Renal Cell Carcinoma*

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### *Upper Tract Urothelial Cell Carcinoma*

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### *Testicular Cancer*

1. Feldman DR, Bosl GJ, Sheinfeld J, et al: Medical treatment of advanced testicular cancer, *JAMA* 299:672–684, 2008.
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### *Penile Carcinoma*

1. Feldman AS, McDougal WS: Long-term outcome of excisional organ sparing surgery for carcinoma of the penis, *J Urol* 186:1303–1307, 2011.
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## CHAPTER 18

# Radiation Therapy

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Neha Vapiwala, MD

In light of excellent disease control achievable with a variety of different treatment modalities, the optimal role of radiation in the curative and palliative management of genitourinary malignancies is one of the more high-profile topics in clinical oncology. Radiation may be used alone as curative treatment of some tumors or as an adjuvant to surgery or in combination with systemic or other chemotherapy. It is also used as salvage local therapy for disease recurrence in the postoperative setting or as a palliative therapy to alleviate symptoms in patients with advanced or metastatic disease. The continued advancement in radiation technology has not only provided new tools to further improve the therapeutic index but has also raised important questions regarding its uses. Appropriate utilization of radiation requires knowledge of its mechanisms and techniques to fully understand the potential and the limitations of this modality.

**X-rays, gamma rays, electrons,** and **proton beams** are types of electromagnetic energy used to treat cancer. First discovered in 1895 by Wilhelm Rontgen, x-rays were rapidly put to use to treat malignancy. In March of 1896, Emil Grubbe, a 21-year-old medical student, irradiated the chest wall of a woman with relapsed breast cancer and was the first to document a local response with radiation. In the early 1900s with the discovery of radium, tumors were implanted with gold wires infused with radium to deliver more focal radiation therapy. Decades later, with the advent of linear accelerators, cyclotrons, and complex computer algorithms, radiation dose can be conformed and adapted to "wrap around" the targeted structure and account for internal motion, all while avoiding critical normal tissues. Some forms of radiation can even be engineered to stop on a dime.

## Physics

Gamma rays are radiation produced by the decay of radioactive isotopes, either natural or man-made, whereas x-rays, or **photons,** are artificially produced when charged particles strike a target. Photons are typically produced in a **linear accelerator** in which electrons are accelerated to hit a tungsten target to emit the photons. When that tungsten target is removed from the path of the beam, **electron** beams are generated; funnellike applicators and collimators can be inserted to help shape the beam. Gamma rays have well-defined energies characteristic of the isotope that emits them, whereas x-rays have a broader spectrum that is determined by the energy of the machine that produced them. **Protons** are heavy charged particles that are accelerated to strike a target and that deliver their energy at a specific point in the tissue. Radiation dose delivered to the body is expressed in gray (**Gy**) or for protons in Gy (relative biologic effectiveness), abbreviated **Gy(RBE**).

For photons, the energy of electromagnetic radiation determines the ability of radiation to penetrate tissue, with higher energies allowing deeper penetration. Higher energies scatter their radiation dose in a more forward direction. In high-energy machines, the maximum dose is deposited below the skin surface. For this reason, a low-energy machine operating at peak energy of 140,000 volts would be preferable in treating superficial tumors such as skin cancer because the maximum dose is deposited in the skin, and the dose decreases exponentially to less than 25% of the maximum dose at a depth of 4 cm. For tumors deeper in the body, a more penetrating beam from a linear accelerator, such as one operating at a peak energy of 10 million to 15 million volts (10-15 MV) is preferable. A 15-MV beam deposits its maximum energy at a depth of 2.8 cm and is still able to deliver 50% of its maximum dose at a depth of 20 cm. Unlike the higher energy photons, electrons deposit their maximum dose at or near the surface, penetrate to a predictable depth with a relatively constant dose, and then decrease rapidly. Protons, on the other hand, deliver their energy at the end of their **Bragg peak**. Like photons, the ability of the proton beam to penetrate deeper in the body depends on its energy. The main difference, however, lies in the exit dose. Photons continue to deliver small amounts of energy over a range. Therefore tissues beyond the target will also receive dose from photon irradiation. Because almost all of the energy in protons is delivered at the end of the Bragg peak, virtually no dose is delivered to tissues beyond that point.

In some situations, it is preferable to deliver radiation to the tumor from an internal source. This technique is known as **brachytherapy**, meaning short-distance therapy. Radiation dose is determined by the ability of the radiation to penetrate tissue and the distance from the source of the radiation. Like visible light, the intensity of the radiation decreases in proportion to the square of the distance from the source ($1/d^2$). Because doubling the distance from the source of radiation will decrease the intensity by 75% and tripling the distance will decrease the intensity by 89%, it is reasonable to consider placing the source of radiation within the tumor to minimize the dose that would be delivered to the surrounding normal tissue.

Radioactive **isotopes** produce radiation with a decreasing dose rate as time passes, a process known as radioactive decay. Every isotope has a **half-life,** defined as the time required for the dose rate to decrease by 50%. Depending on the half-life, certain isotopes are used for either **high-dose rate (HDR) brachytherapy** or **low-dose rate (LDR) brachytherapy**. For HDR, an applicator or catheter is inserted into the target structure, and the radioactive isotope is inserted for a specific amount of time (usually a few minutes) and then removed. The procedure can be repeated as often as needed to deliver the adequate total dose. In LDR, the isotope is left in the applicator for several hours to days or may be inserted directly into the target organ and left there permanently.

## Radiobiology

Radiation causes its effects in tissue by producing ionizations within the cell. The target in cells is the DNA molecule, and the ionizations will produce breaks in the DNA strand. Nonmalignant, healthy cells can repair this damage if it is confined to a single strand because the opposite strand serves as a template for repair. However, if two strand breaks occur on opposite chains in close proximity, the two ends of the chromosome may drift apart. These fragmented chromosomes may adhere to other chromosomes or they may sort out randomly when the cell divides, resulting in the daughter cells to be missing critical segments of DNA or have excess and unregulated copies of other genes, either of which may be fatal to the cell. Thus the damaged cells are observed to die a mitotic death; the lethal effect of radiation is not expressed until the cell replicates.

Radiobiologic research is ongoing to identify factors that affect the survival of cells and methods to selectively increase radiation effects on tumor cells. The easiest method to assay the effect of radiation is to deliver a dose of radiation to a suspension of single cells and then measure the percentage of surviving cells. The technique uses a suspension with a known concentration of cells. A sample is placed on a culture plate and the colonies are counted. At the same time a similar-sized sample is radiated and plated and the number of colonies counted. The ratio of the number of colonies developing on the two plates is the surviving fraction.

Because a Gy represents a specific amount of energy transferred to tissue, each Gy in theory should have an equal physical effect on the cell. However, the biologic effect is less for the first Gy than it is for the 101st Gy, suggesting that cells are capable of accumulating a certain amount of damage that is not lethal. Interestingly, if the radiation dose is split up and delivered over several **fractions** with time between fractions for cells to repair the damage, each fraction of radiation will kill the same proportion of the surviving cells. If the cells are allowed to completely repair the damage from the first dose, the second dose of radiation will have the same effect on the surviving cells as it would have if they had never been radiated the first time. This effect demonstrates the importance of uninterrupted radiation treatments. In vitro studies have shown normal cells to repair radiation-induced damage more efficiently than tumor cells, and attempts to deliver two doses of radiation per day, known as **hyperfractionation,** may increase the efficacy of treatment.

Oxygen is known to enhance the effects of radiation both in vivo and in vitro. Cells are more sensitive when radiated under oxygenated conditions than when they are hypoxic. Normal tissues are always oxygenated, but experimental measurements in tumors have shown that these cells pile up around a capillary and consume the available oxygen, limiting diffusion into the deeper tissues. This scenario results in well-oxygenated, relatively sensitive cells adjacent to the capillary and necrotic material at a distance away from the capillary. Between these two areas is a region of viable but hypoxic cells that are more resistant to radiation. In vitro studies show that hypoxic cells require 1.5 to three times as much radiation to achieve the same cell kill.

Current efforts are being taken to develop substances that act like oxygen in cells but are not metabolized like oxygen. Ideally, these substances will help to deal with the problem of hypoxic tumor cells without affecting the sensitivity of normal cells. In vitro work showed that these compounds, known as **radiosensitizers,** sensitized hypoxic tumor cells to the effects of radiation. However, clinical trials were limited by toxicity. Similarly, efforts to develop drugs that protect normal cells from the effects of radiation are underway. Although these trials also have failed to show in vivo benefit, efforts continue to develop a new generation of sensitizers and protectors. More importantly, chemotherapy and hormonal therapies have been observed to affect tumor sensitivity in vivo, and these agents form the basis of many current combined modality trials.

## Treatment Planning

The delivery of radiation to a tumor requires a physician to perform five functions: (1) identify and locate the structures to be treated, (2) identify those adjacent structures that need to be protected, (3) prescribe the appropriate dose of radiation for the tumor based on its size and histology, (4) consider the tolerance of tissue within the target that may be affected by treatment, and (5) consider the tolerance of tissues between the skin and the target (transit volume). Although a complex but solvable problem, most clinical situations require some compromise on one or more issues. The clinician must select those compromises that will minimize effects on normal tissue while maximizing the probability of tumor control, known as the ***therapeutic ratio***.

Modern equipment and computer software allow for sophisticated **three-dimensional conformal radiation treatment (3D-CRT)** and **intensity modulated radiation therapy (IMRT)**. Both of these techniques have become the standard of care in most radiation oncology centers. Patients undergo computed tomography (CT)-based simulation in which a series of axial images are obtained of the target and the adjacent critical structures. Often fiducial markers are placed prior to simulation in the target organ to improve target localization during the treatments. The target or targets, depending on other areas at risk for tumor involvement, bony structures, and sensitive normal tissues, are defined on the CT imaging. Today's treatment machines are able to deliver radiation from a wide range of angles to specifically shape dose intensities to conform around the target.

For example, in the treatment of prostate cancer, newer techniques using IMRT are able to reduce the dose exposure to normal tissues and allow for higher doses to be delivered to the prostate without increased complications. Computers are used to plan the delivery of radiation using several smaller radiation fields, known as ***beamlets***, from different beam directions. Each beamlet treats only a portion of the prostate, but when the dose intensity from all of the beamlets are added together, the entire prostate receives the full dose with slight inhomogeneity, while reducing the volume of normal tissue receiving a high dose. Although the part or the entire target receives the maximal dose, a larger volume of normal tissue is exposed to a small amount of radiation. Figure 18-e1 A-D

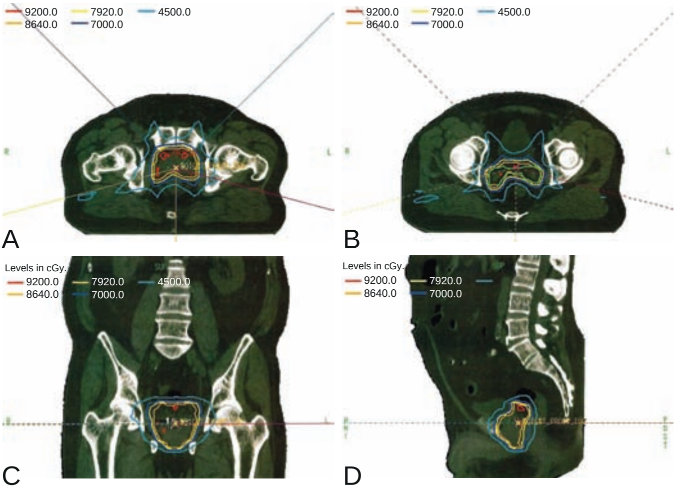

FIGURE 18-e1 A-D **A and B.** Transaxial slice of a prostate plan demonstrating the culmination of dose at the target volume that includes the prostate and seminal vesicles. **C.** Coronal view of the isodose lines demonstrating sparing of the femoral heads bilaterally. **D.** Sagittal view demonstrating the shape of the dose to avoid the rectum and bladder. The entire prostate and seminal vesicles are getting over 8000 cGy as demonstrated by the isodose lines.

shows the dose distribution around the target and the nearby organs. Because of the decreased exposure to normal tissues, higher and more effective doses can be delivered to the target with patients experiencing fewer side effects. As with conventional radiation delivery techniques, patient positioning is extremely critical in the delivery of IMRT; these techniques require consistent localization and patient positioning to allow tighter margins and potentially deliver higher doses. Immobilization casts or molds, rectal balloons, and fiducial markers are all tools used to assist in proper targeting of the radiation to the desired location. An alternative method is to deliver the radiation from within the tumor using interstitial radiation, or brachytherapy. LDR permanent implants in prostate cancer typically use radioactive seeds containing iodine or palladium isotopes. The patient is taken to the operating room, where epidural, spinal or general anesthesia is administered and the patient is placed in the lithotomy position. Using transrectal ultrasound guidance, hollow needles are placed through the perineum into the prostate, and the radioactive seeds are deposited interstitially. The needles are removed after the procedure. Seed positions within the prostate are determined prior to the procedure using reconstructed images from sophisticated CT, MRI, and/or ultrasound planning equipment. Intraoperative planning can also be accomplished with the assistance of a physicist in the operating room, allowing for real-time modification of the treatment plan at the time of the procedure to ensure accurate placement of seeds. After the procedure, reimaging confirms seed placement, and the quality of the implant can be judged. Figure 18-e2A shows axial slices through the prostate demonstrating the placement of seeds in the prostate. Figure 18-e2B shows a 3-D reconstruction of the prostate obtained from the postimplant CT scan demonstrating radioactive dose clouds from the seeds within the prostate. Although the implant delivers lower doses to the periprostatic tissues, substantially higher doses are delivered to the interior of the prostate.

As with LDR brachytherapy, in HDR brachytherapy the patient is sedated and anesthetized, after which hollow catheters are inserted percutaneously through the perineum into the prostate. A radiation plan is designed based on the 3-D rendering of the prostate, rectum, urethra, bladder, and catheters through which the radioactive sources will travel, with a goal of emitting adequate

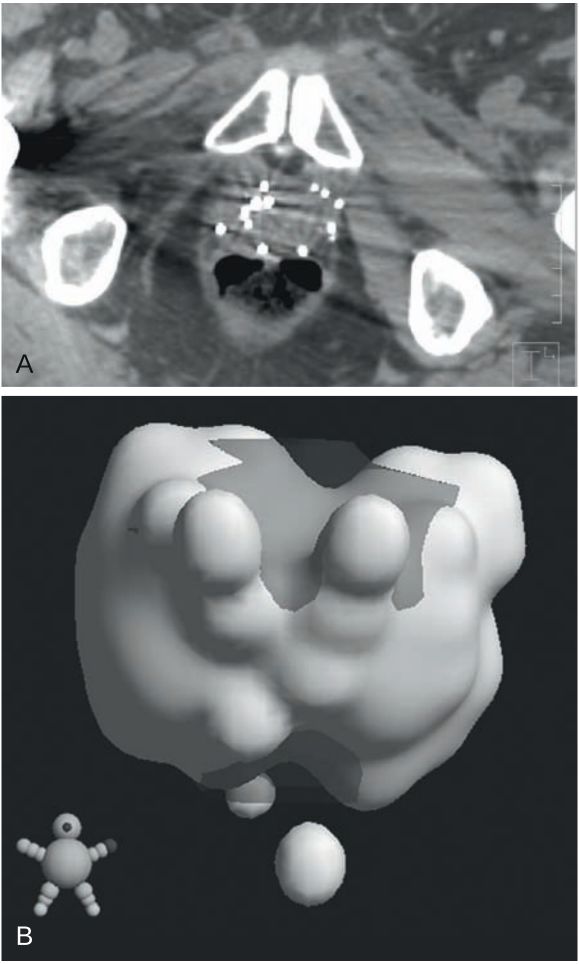

FIGURE 18-e2 A-B **A.** Transaxial slices through the prostate of an LDR brachytherapy plan. The radioactive seeds appear as high-density spots that can be counted. The prostate is contoured on the axial CT slices, and the relation of seed positions to the prostate gland is used to analyze the dose delivered. **B.** Dose-delivery calculation in a 3-D reconstructed image. The prostate gland is shown in the darker gray, and the dose contribution from each seed is shown as the light gray spheres. The conglomeration of spheres results in a dose cloud that ideally envelopes the prostate.

dose throughout the prostate gland from the designated positions. The radiation oncologist can preferentially deliver a higher dose to certain parts of the organ, while sparing critical areas such as tissue surrounding the urethra. Images of HDR brachytherapy of the prostate are shown in Figure 18-e3 A-C.

Because many prostate tumors have some degree of extracapsular extension (ECE), the reduced periprostatic dose may not effectively treat the tumor volume. Patients with very large prostate glands may have anatomical constraints because of the pelvic

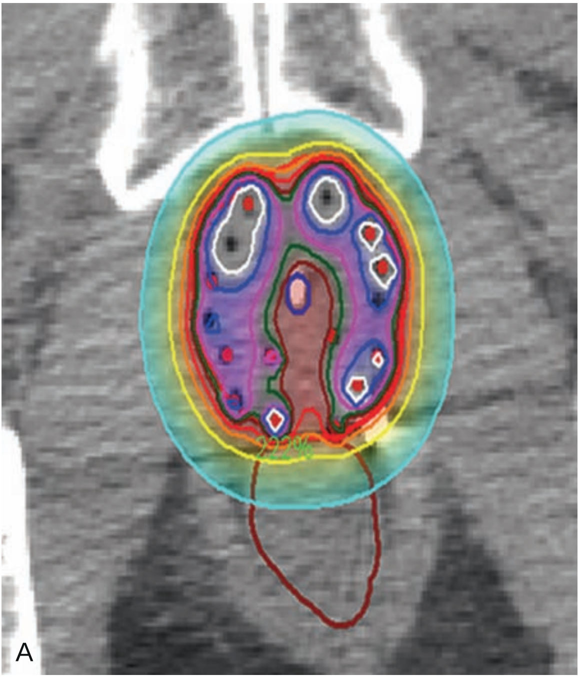

FIGURE 18-e3 A-C **A.** Transaxial slice through prostate with HDR applicator showing isodoses in color wash. Note sparing of the urethra. **B.** Transaxial slice through prostate with HDR applicator catheters demonstrating dose cloud. **C.** 3-D reconstruction of dose-delivery calculation from plan shown in B. Bladder contoured in yellow; rectum contoured in green; prostate dose contoured in red; urethra with contrast contoured in dark blue; filler space between prostate and rectum contoured in light blue.

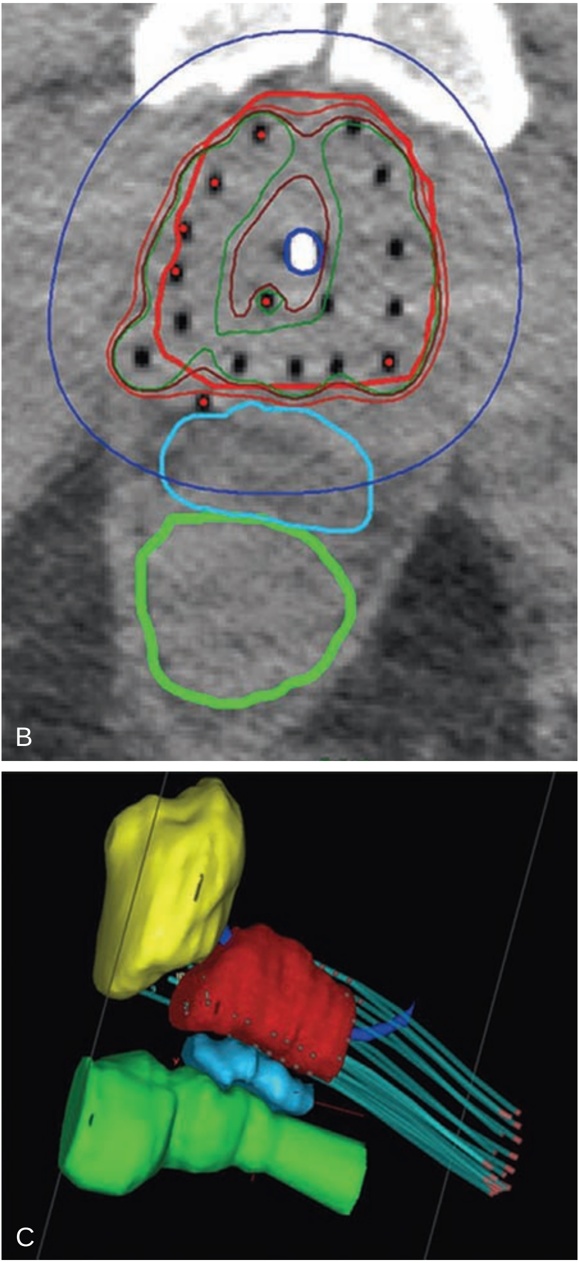

FIGURE 18-e3—cont'd

bones (i.e., pubic arch interference) that could limit placement of the needles or applicators. However, with appropriate intraoperative positioning techniques, many larger prostates can be implanted. With HDR brachytherapy, radiation doses can be delivered beyond 3 mm, which is the distance from the capsule that 90% of microscopic ECE extends. Furthermore, Merrick et al demonstrated that prostates greater than 60 cc had no greater risk of postimplant obstruction.

# Clinical Radiation Oncology

## RENAL PELVIC AND URETERAL CARCINOMA

The role of radiation for renal cancers is currently evolving with ongoing studies looking at **stereotactic radiosurgery** for unresectable tumors. Furthermore, the use of radiation in the treatment of patients following resection remains controversial. Among patients with tumor transgressing the renal capsule, the risk of local recurrence is high. Rafla et al reviewed his experience and found an apparent benefit to the use of adjuvant radiation therapy for patients with involvement of the renal capsule (T3). Among patients receiving adjuvant radiation, the 5-year survival was 57% compared to 28% for patients treated with surgery alone. It is presumed that the improved survival was related to the reduced incidence of local recurrence, although this finding could not be documented because these patients were treated in the pre-CT era. In contrast, subsequent trials reported by Finney et al and Kjaer et al found no benefit with adjuvant radiation. The results of the Finney trial although limited by the small number of patients, demonstrated an 8% treatment-related mortality as a result of liver injury in the radiation arm. The results reported by Kjaer are clouded by the registration of node-positive patients in whom Rafla demonstrated no benefit. This study also was complicated by the fact that 16% of the patients randomized to radiation did not receive radiation and those patients who were treated experienced a 44% incidence of major toxicity. Both Finney and Kjaer used anterior and posterior fields, and the toxicity occurred in patients with right-sided tumors. In such cases, large parts of the liver were treated to 45 Gy, which is well above liver tolerance. Because many tumors today are found incidentally at the time of a diagnostic CT scan for other reasons, it is not clear that these patients have the same prognosis after surgery as patients in these older studies who presented with hematuria, mass, or other more advanced findings. Given the potential serious side effects and little data demonstrating a benefit, radiation is not generally indicated in the adjuvant setting for renal cell cancers.

Radiation, however, is often used for metastatic renal cell carcinoma to palliate bleeding, pain, or neurologic symptoms related to spinal or central nervous system (CNS) involvement. These tumors have traditionally been thought to be radioresistant, arguing for surgical excision of limited metastatic disease. In a review of their experiences, Onufrey and Halpern reported that although these tumors tended to respond slowly and did not seem to respond to higher doses of radiation, patients still achieved good palliation of symptoms in most cases. Zelefsky et al and Yamada et al have demonstrated that renal cell carcinomas can respond to higher hypofractionated radiation doses in the range of those typically used with stereotactic body radiation therapy.

Data are very limited on the use of radiation to manage tumors in the renal pelvis and ureter. The rationale that supports the use of radiation is based on the anatomy of the retroperitoneum as it affects the surgical resection. Tumors of the renal pelvis and ureter are resected with wide proximal and distal margins. Because these tumors are frequently multifocal and can spread along the urothelium, the resection includes the kidney and a generous bladder cuff. The radial margin, however, is more problematic, and radiation may be indicated to sterilize any tumor in this region. The thin wall of the ureter is the only barrier to lateral spread of the tumor, and the surgeon is limited in the ability to laterally extend the dissection. No additional barriers for tumor spread in the retroperitoneum exist. There have been no recent reports of the use of radiation in the postoperative setting, but an older report from the University of Texas MD Anderson Cancer Center described 8 out of 58 patients who underwent nephroureterectomy for transitional cell carcinoma who were thought to have a high risk for local recurrence. The proximal and distal margins of resection were negative, but because of the thin wall of the ureter and the transmural extension of the tumor, there was concern that the radial margin may not have been adequate. These eight patients received 40 to 60 Gy of radiation to the ureteral bed with no major morbidity reported, although most of the patients developed anorexia, nausea, and diarrhea. Four of the eight patients died with a tumor, but only one of these patients had a recurrence of a tumor in the retroperitoneum. Extrapolating these findings to tumors in the renal pelvis would suggest that patients with transitional cell carcinomas lower in the pelvis or extending into perinephric fat may benefit from adjuvant radiation.

The fields that have been used in patients with renal pelvis tumors encompass the nephrectomy bed, lymph-node drainage sites, surgical clips, and scar. Although there is no proven benefit to adjunctive radiation in patients with lymph node metastases, these nodes are frequently sampled in conjunction with the nephrectomy, so there is concern about possible contamination of the medial structures. Therefore including the preaortic, para-aortic, and paracaval lymph nodes in the treatment field is reasonable. Ureteral tumors are generally treated with fields that extend proximally and distally to encompass the preoperative tumor volume with a 5- to 7-cm margin. The medial and lateral margins are determined by the surgical resection and the gross lateral extent of the tumor, although the prevertebral structures are generally not included. Unfortunately, because of the sensitivity of the small bowel to radiation, doses to this area are limited. Therefore radiation in this setting is not typically done except in rare circumstances.

## BLADDER CARCINOMA

Radiation in the management of transitional cell carcinoma of the bladder (TCCB) can be an effective treatment option, although the "gold standard" for invasive bladder cancer remains radical cystectomy. Radiation was initially used prior to cystectomy to increase the probability of successful cystectomy. At the Memorial Sloan-Kettering Cancer Center (MSKCC) a substantial number of patients, mostly with T3b and T4 tumors or poorly differentiated tumors, were taken to cystectomy but did not complete the procedure because of the presence of extravesical extension or lymphadenopathy. They developed a policy in which these patients received a dose of 40 Gy in 4 weeks with a 4-week break prior to resection. Intraoperatively, many of these patients were found to have substantial regression of tumor and were able to have a greater probability of complete resection and a reduction in the risk of pelvic recurrence. However, the surgical procedure was more difficult because the radiation-induced fibrosis limited the amount of ureter that could be used in the urinary reconstruction. Because many of these patients had such dramatic responses, they attempted definitive treatment of bladder carcinoma with radiation alone. Some patients received further radiation to a total dose of 60 Gy with the intent of achieving tumor control, although the 4-week break did reduce the efficacy of radiation compared to 60 Gy of continuous radiation over 6 weeks.

Subsequently, a dose of 20 Gy in 1 week was attempted during the week prior to surgery. There was less fibrosis, but no change in the complication rate. Subsequent to the MSKCC report, Montie et al at the Cleveland Clinic and Skinner and Lieskovsky at the University of Southern California reviewed their experience and found that patients treated with surgery alone had the same survival and pelvic recurrence rates as patients treated with preoperative radiation. Montie et al selected patients who were thought to be at high risk for local recurrence, referred them to receive adjuvant radiation, and excluded them from the analysis. This may bias the analysis by excluding patients who were thought to have a poorer prognosis. Many of the patients reported by Skinner received adjuvant chemotherapy, and it is not clear whether the results indicate that there is no benefit from adjuvant radiation or whether a similar effect can be achieved with adjuvant chemotherapy. The INT-0080 trial demonstrated a survival benefit and higher rates of a complete pathological response with neoadjuvant chemotherapy in patients with T2-4a bladder tumors.

Although a large meta-analysis by Parsons et al showed a survival benefit with preoperative radiation in patients with clinical T3 tumors, this analysis has been criticized. The trials that did not meet the criteria for inclusion generally supported the use of surgery alone; most of them were not randomized, or critical parameters were not reported. The largest single-institution experience with preoperative radiotherapy for bladder cancer was done at the MD Anderson Cancer Center. Among 338 patients with T2 to T4 disease, 50 Gy was delivered and followed by radical cystectomy at 4 to 6 weeks. Pathologic downstaging occurred in 65% of cases, and 42% had no tumor in the surgical specimen. Pelvic and distant recurrence rates were 16% and 43%, respectively. A meta-analysis on neoadjuvant radiation demonstrated no effect on survival; therefore more effective chemo was preferred to preoperative radiation.

In Europe and Canada, the initial focus of treatment was to use radiation as the primary modality and to deliver high-dose external-beam radiation in an attempt to preserve the bladder and sterilize the tumor. These experiences showed that the local control rates are only 35% to 45% in T2 tumors and even poorer for patients with T3-4 tumors. Compared to patients undergoing cystectomy, in whom survival rates are approximately 75% in T2 tumors and 50% to 65% for patients with T3 tumors, radiation appears to be inferior.

Interstitial radiation has been used by a number of centers to treat bladder tumors and deliver a higher dose to a small portion of the bladder with relative sparing of the rectum and the rest of the bladder. Van der Werf-Messing treated patients with three fractions of 3.5 Gy to reduce the risk of intraoperative tumor dissemination and then carried out a surgical incision into the urinary bladder to perform a radium needle implant under direct vision. The sources were attached to suture material that was brought out through a stab wound adjacent to the incision. The sources were left in place to deliver a dose of 70 Gy in 7 to 8 days; after that, they were removed through the stab wound. This reduced the risk of local recurrence in T1 or T2 tumors from 75% to 18% and reduced the need for cystectomy from 65% to 20%. A similar reduction was seen in the 10-year risk of metastatic tumor from 50% to 18%. For more extensive low-grade tumors, including larger T2 tumors and small T3 tumors, a preimplant dose of 30 Gy was delivered in 3 weeks to the pelvis and then an additional 45 Gy with the implant. This dose treated any subclinical disease that may have extended beyond the high-dose implant volume and also delivered a higher dose to the larger gross tumor. The local control in this group was 92% with an actuarial disease-free survival of 74%.

In the United States there has been an interest in chemosensitized radiation in treating a number of tumors based on the theories advanced by Steele and Peckham. Chemotherapy can reduce the tumor burden so that radiation may deal more effectively with the residual tumor. Similarly, spatial cooperation may allow the radiation to deal effectively with the bladder tumor, whereas systemic chemotherapy may treat subclinical metastatic tumor.

The National Bladder Cancer Cooperative Group (NBCCG) in the United States and the group in Innsbruck, Austria, sponsored trials delivering cisplatin on days 1, 22, and 43 of radiation following transurethral resection of bladder tumor (TURBT) with reevaluation after 40 Gy had been delivered. Patients with less than visual complete responses after 40 Gy were sent to cystectomy because researchers found it was unlikely that these patients would achieve a complete response with an additional 20 to 25 Gy. Among patients with complete responses or only positive cytology who received an additional

20 to 25 Gy, the 2-year relapse-free survivals were 68% and 53% in the Innsbruck and NBCCG trials, respectively. In an effort to improve the results with conservative surgery and chemosensitized radiation, the NBCCG and Radiation Therapy Oncology Group (RTOG) began a joint trial delivering two cycles of *methotrexate, vinblastine, and cisplatin (MVC)* prior to radiation-cisplatin therapy. The 4-year survival with bladder conservation was 44% and the overall survival was 62%. A subsequent trial randomized patients to neoadjuvant chemotherapy prior to chemosensitized radiation versus immediate chemosensitized radiation; no benefit to the neoadjuvant therapy was observed.

To evaluate the role of definitive radiation therapy for bladder cancer, Shipley and colleagues prospectively studied 190 patients with muscle-invasive T2-4a bladder cancers. After maximal transurethral resection of the bladder tumor, patients were treated with 40 Gy to bladder with chemotherapy and then reevaluated by repeated biopsy and urine cytology. The tumor response guided subsequent therapy. Patients with a complete response or who were medically unfit for cystectomy received additional radiation to a total dose of 64 to 65 Gy. Patients without a complete response underwent radical cystectomy. A total of 66 patients (35%) ultimately underwent radical cystectomy. In all, 60% of patients treated with chemoradiation alone had long-term control of their bladder cancer. Superficial disease recurred in the bladder in 24 patients; in most cases, it was managed conservatively by means of further resection and/or intravesical chemotherapy. Muscle invasive recurrence developed in 16%. The 10-year cause-specific survival rates were 60% overall and 45% with an intact bladder. These findings suggest further study with dose escalation or more radiosensitizing chemotherapy is warranted for bladder preservation in bladder cancer. A recent report from Azuma et al from Japan demonstrated over 70% complete responses in patients with locally advanced bladder cancer with the use of a balloon-occluded arterial infusion of cisplatin and gemcitabine with concomitant hemodialysis and concurrent radiation therapy.

Unless gross disease is left behind after cystectomy, adjuvant radiation is rarely given. An Egyptian study randomized patients to postoperative radiation or observation for patients with squamous cell carcinoma and found a decrease from 50% to 10% of pelvic recurrences. However, extrapolation of findings to patients with transitional cell histology is not appropriate.

The utility of bladder conservation has sharply declined because surgical techniques have significantly improved continent diversions and allow for better quality of life by preserving normal voiding function and potency in men. Women and some men will intermittently catheterize an internal reservoir, which is much easier than maintaining an external appliance. In institutions with the availability of continent diversions, chemosensitized radiation is generally reserved for patients with unresectable tumors or patients unable or unwilling to undergo cystectomy. Risks of radiation include rectal ulcers (7%), bladder contracture (10%), impotence in men (greater than 50%), and bowel injury (3%).

## PROSTATE CANCER

As challenging as the treatment decisions may appear in patients with bladder cancer, the discussions surrounding the ideal management of prostate cancer are far more heated. With the advent of prostate-specific antigen (PSA) screening, the incidence of prostate cancer has skyrocketed to more than 200,000 new cases per year. Many of these tumors are probably not clinically significant because a high prevalence of occult prostate cancer is found incidentally in autopsy series. Screening asymptomatic men with no clinical signs of prostate cancer is also controversial. Having said this, it remains difficult to reliably distinguish men with incidental tumors from those with clinically significant tumors, and the number of deaths from prostate cancer in the United States still stands at almost 30,000 per year.

The critical elements in evaluating a man with prostate cancer require that the clinician estimate the annual risk of tumor dissemination and tumor-related mortality and the annual nonprostate cancer-related mortality for the individual. In completing an ad hoc risk-benefit analysis, it is necessary to factor into the equation any conditions that may increase the risk of radiation-related morbidity, including prior abdominal surgeries, any history of peritonitis or pelvic inflammatory conditions, such as Crohn disease or ulcerative colitis, or a history of diverticulitis.

It is necessary to have the proper equipment to deliver radiation for prostate cancer. CT-based treatment planning, 3D-CRT and IMRT, and escalation of the dose to the prostate past 70 Gy have become standard at modern radiation oncology centers. Proton therapy centers are increasing throughout the United States, but proton therapy's superiority over IMRT has yet to be fully demonstrated. Accurate localization and patient and target immobilization techniques have become more crucial as the dose delivered by more advanced radiation methods continues to escalate.

Radiation doses to target structures are often limited by nearby critical normal structures. Prior to CT-based planning, the bladder and rectum could only be visualized by the insertion of contrast material in these organs and visualizing on radiographs. Radiation treatment plans often erred on underdosing the tumor to avoid long-term toxicity or morbidity. With the advent of CT-based planning, the radiation oncologist is able to outline the prostate, bladder, rectum, and femoral heads to locate in three dimensions the edges of each of the organs. Computer-assisted planning allows various shapes of beams to be generated, each of which helps to conform the dose to the target while minimizing doses to the bladder and rectum. With IMRT and sophisticated planning software, radiation oncologists have been escalating the dose delivered to the prostate over the past few decades as their ability to spare the critical organs continues to improve.

A radiation treatment plan must be evaluated by the radiation oncologist to determine if certain dose constraints are met. The **RTOG** has published a series of recommended dose constraints on critical organs, namely the rectum, bladder, femoral heads, and penile bulb that should have minimal morbidity to prostate cancer patients. Careful examination of the dose volume histogram (DVH) for each treatment plan will ensure these constraints are met and patients will be treated safely. Figure 18-1 shows the **DVH** for the prostate, bladder, and rectum of a patient being treated for prostate cancer. A dose of 86.4 Gy was prescribed to the prostate and seminal vesicles plus a small margin; 95% of entire target volume received a minimum dose of 84 Gy, but a small fraction of the prostate received higher doses. The mean dose through the prostate is fairly homogenous. Likewise, similar histograms for the rectum and bladder demonstrate the maximum and minimum doses delivered to each organ. Whereas a small volume of rectum will

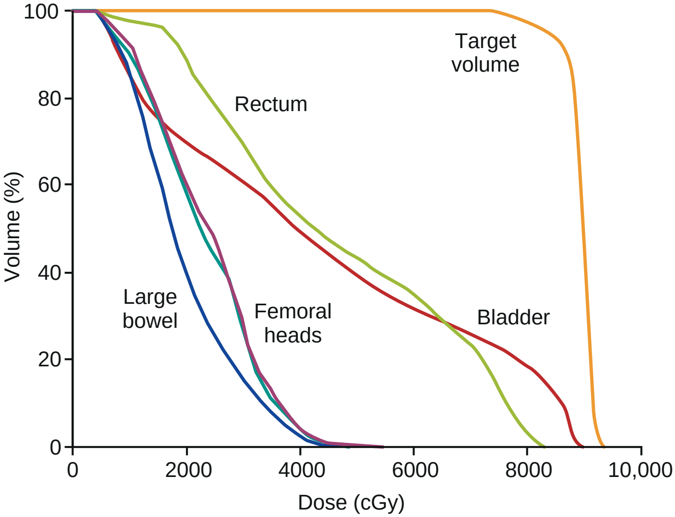

FIGURE 18-1 Dose volume histogram (DVH) demonstrating the dose delivered to the target organ (prostate and proximal seminal vesicles) and organs at risk (bladder, rectum, large bowel, and femoral heads) is shown here. The goal in evaluating radiation treatment plans is to maximize the dose to the maximum volume of the target while minimizing the dose to normal structures.

tolerate high doses of radiation, the graph shows that most of the rectum receives a much lower dose. In this histogram 50% of the rectum received less than 45 Gy.

The maximum radiation dose tolerated by the prostate continues to evolve. Although some centers use doses of 74 to 81 Gy, others such as Memorial Sloan-Kettering and the University of Michigan are exploring doses of 84 to 91 Gy, utilizing the concept of dose escalation. Between October 1988 and December 1998, Zelefsky et al treated more than 1000 patients with clinical stages T1c-T3 prostate cancer with either 64.8 to 70.2 Gy or 75.6 to 86.4 Gy. Five-year actuarial PSA relapse-free survival was significantly improved with the higher dose. However, questions remained, including whether PSA control had effected an improved overall survival, and did the improved PSA control outweigh the higher toxicity observed with the higher doses.

The use of higher doses has necessitated tighter margins to minimize dose to neighboring tissues but not compromise adequate coverage of the tumor. This combination requires precise prostate localization, which in turn requires both external and internal organ immobilization. To achieve this and further improve upon the precision of treatment delivery, many centers have adopted individualized immobilization devices, such as body casts and knee-foot locks, and placement of intraprostatic fiducial markers and other specialized techniques to predict and/or reduce organ motion. Most techniques focus on patient alignment and target localization just prior to treatment delivery. However, the prostate can often move during the radiation treatment itself because of physiologic reasons such as gas in the rectum; thus there is a risk that the targeted prostate may move out of the irradiated area during the radiation delivery. To combat this intrafraction movement, fiducial markers fitted with transponder technology can be implanted transrectally into the prostate. These beacons, each about the size of a rice grain, communicate with the treating therapist's console and allow 3-D tracking of the prostate position in real time. The radiation beams can be adjusted accordingly. Monitoring the target position before each radiation treatment is known *as* ***image guided radiation therapy (IGRT)*****.**

In the 1950s particle accelerators were developed that could accelerate heavier particles such as protons. Protons were put to use in the treatment of cancer at the Harvard Cyclotron Laboratory in 1961. Since then, multiple facilities offering proton therapy have sprouted throughout Europe, Asia, and the United States. The physical advantages of proton therapy over standard photons are that proton beams have very little entry dose, a maximal peak dose (known as the Bragg peak) that can be "dialed up" to a specific location in the body, and virtually no exit dose beyond the Bragg peak. These characteristics potentially allow more sparing of the tissues outside of the target volume than is possible with IMRT or IGRT techniques. Figure 18-2 shows a transaxial slice of a prostate being treated with two opposing proton beams. Each beam delivers minimal dose on entry and virtually no dose beyond the distal edge of the target structure. Studies have shown modest improvements in bladder and rectal toxicity rates with proton therapy. However, no randomized data that compare outcomes for patients treated with IMRT and proton

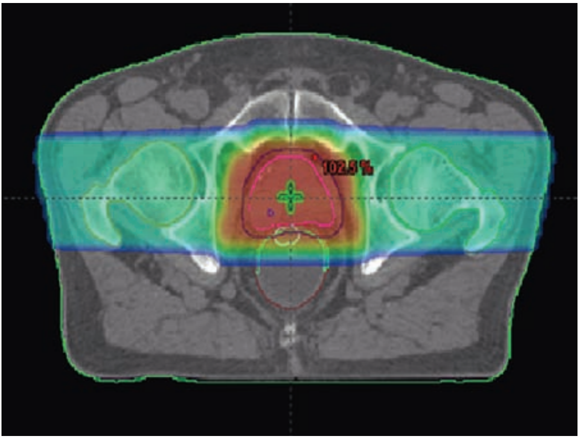

FIGURE 18-2 Radiation treatment plan of prostate using opposed proton fields. Virtually no dose enters or exits through the rectum or bladder.

therapy for prostate cancer have been reported. Furthermore, the cost of erecting and maintaining a proton facility continues to be prohibitively expensive.

In comparing the results from different series, it is necessary to compare the definitions of tumor control and treatment-related morbidity. There is no universally accepted definition of biochemical control after radiation as there is after surgery. Following surgery, PSA should be undetectable because all prostatic tissue has been theoretically removed. However, following radiation the residual normal prostate epithelium will continue to produce PSA. The latest consensus from the **American Society of Therapeutic Radiology Oncology** (**ASTRO**) is nadir following radiation + 2 ng/mL defines treatment failure. Often following radiation, a PSA bounce is observed. A **PSA bounce** is a temporary PSA rise after the initial postradiation PSA drop. The etiology is not clear, but occurs about 18 months (range 6 to 36 months) after radiation. If the clinician is too sensitive to the results of the serum PSA, the risk of recurrence may be overestimated.

Grading of radiation-induced side effects is also subject to a lack of uniformity. Individuals who have had radiation may develop painless rectal bleeding, and proctoscopy often reveals mucosal atrophy and telangiectasias. Many physicians would score this effect as a minimal or grade I toxicity, whereas others would score it as grade II toxicity because they may have a lower threshold to recommend symptomatic treatment. Some studies have also considered rectal hemorrhage requiring transfusion or laser ablation of the anterior rectal wall as grade II toxicity, whereas others consider it grade IV (life-threatening) toxicity. Similarly, men who advise their physicians that they are able to obtain partial erections may be considered by some physicians to be potent, although they are not able to achieve penetration. Others require that men be able to sustain an erection and reach orgasm.

Furthermore, controversy in the treatment of prostate cancer exists over the definition of the target volume. Many institutions will deliver a dose of 45 Gy to the obturator, hypogastric, external iliac, and common iliac lymph nodes and boost the prostate to the final total dose of greater than 76 Gy. Others will treat the prostate only, with or without part or all of the seminal vesicles. Debate continues on the benefits of pelvic nodal irradiation. Roach et al reported on data from the RTOG 9413 trial in which patients with an estimated greater than 15% risk of lymph nodal involvement were treated to the pelvic nodal areas or to the prostate only. Although rectal toxicity in the pelvic irradiation arm was slightly higher, there was an improved progression-free survival at 7 years of follow-up (40% versus 27%) with pelvic radiation. IMRT is now routinely used to treat the pelvic nodes and spare bowel toxicity. A volume of 1 to 2 cm around the iliac vessels is expanded during the simulation and is targeted for treatment planning.

Treatment to only the prostate gland for low-risk disease or after pelvic irradiation encompasses the prostate as defined by treatment-planning CT scan, the proximal prostatic urethra, and some portion of the seminal vesicles. Some clinicians will include the entire seminal vesicles in the treatment volume, whereas others will spare them if no clinical concern of invasion exists. Occult seminal vesicle involvement occurs in 20% to 30% of men with stage T2 prostate cancer and in approximately 50% to 70% of men with T3-T4 prostate cancer. If this portion of the tumor is not treated, then the tumor cannot be cured; but when the seminal vesicles are included, the amount of rectum in the treatment field will increase and cause additional morbidity. MRI with an endorectal coil is extremely sensitive in detecting extent of disease for both extracapsular extension and seminal vesicle invasion.

Although node-positive prostate cancer has become less frequent in this era of community screening, controversy remains over the treatment of node-positive disease. Because these patients have such a high rate of distant metastases, many oncologists may not recommend local therapy. A review of the results in patients with conservatively treated prostate cancer shows a significant risk of bladder outlet obstruction, bladder invasion, hemorrhage, and pain, which may be prevented with radiation. Furthermore, radiation may offer the opportunity to "debulk" the tumor, leaving a smaller tumor burden to be treated by the hormones. Therefore radiation therapy should be considered in patients with advanced disease who are at risk for local progression that may lead to significant morbidity of their cancer.

Men with earlier stage prostate cancer can choose among three accepted treatments: radical prostatectomy, external beam radiation, or interstitial therapy. In reviewing a large series of men, most physicians divide patients into three groups. The group with a low risk of recurrence within 5 years consists of men with tumors confined to less than one half of one lobe of the gland, PSA less than 10 ng/mL, and a Gleason score less than 6. The intermediate-risk group has tumors greater than one half of one lobe of the gland but not involving the other lobe, PSA between 10 and 20 ng/mL, or a Gleason score of 7. The high-risk group has tumors involving both lobes of the gland, extracapsular extension, a PSA greater than 20 ng/mL, or a Gleason score greater than 8. In one analysis comparing these three treatments in the three risk groups, D'Amico found no difference in the relative risk of recurrence between the treatments in the low-risk population. Among intermediate- and high-risk patients there was a threefold higher risk of recurrence among men undergoing interstitial therapy when compared to external beam or surgery, although the difference disappeared in the intermediate-risk group when men were treated with 6 months of androgen deprivation therapy in addition to the implant. In fact, in this intermediate-risk group of patients, D'Amico demonstrated a 10% overall survival benefit at 5 years with the addition of 6 months of androgen deprivation therapy to external beam radiation. Among men with high-risk cancers, the risk of recurrence was greater than 65% in all of the treatment groups, but the recurrences occurred earlier after interstitial therapy than with surgery or external radiation. These results suggest that local treatment is not adequate in patients with higher risk disease and that possibly combining current therapies with androgen deprivation or introducing new therapies such as cytotoxic chemotherapy, higher radiation doses, or more extensive surgery would benefit this population.

There is a spectrum of androgen sensitivity in prostate tumors at diagnosis, and hormonal therapy exposure may select the androgen-independent population to proliferate while the more androgen-dependent population involutes and enters an extended $G_0$ state or undergoes apoptosis. In men with locally advanced, nonmetastatic prostate cancer treated with deferred therapy and androgen deprivation at the time of symptomatic progression, the median time to develop a hormone-resistant tumor was 48 months, whereas men treated with immediate androgen deprivation did not develop a hormone-independent tumor until a median of 84 months after diagnosis. These findings argue for earlier intervention at the time of diagnosis. The most common sites of progression when androgen resistance develops are at sites of previous disease. Therefore, at the University of Pennsylvania, men at high risk are treated with concurrent hormones and radiation to address both the pelvic tumor and occult distant metastatic disease. In a series of 80 patients with a median follow-up of 5 years, the 12-year cancer-specific survival was 90% and the biochemical relapse-free survival was 57%.

The use of combined hormonal and radiation therapy has been prospectively studied in multiple studies. The earliest study from MD Anderson demonstrated comparable 10-year survivals among men with T3 tumors treated with radiation including the pelvic lymph nodes with or without lifelong adjuvant diethylstilbestrol (DES) 5 mg/day. A review of these results found an excess of cardiovascular deaths in the hormone group and an excess of cancer-related deaths in the control group. Two subsequent RTOG trials randomized men to radiation with or without hormone therapy and found that the hormones prolonged disease-free survival. One study treated men with 4 months of androgen-deprivation therapy using a luteinizing hormone-releasing hormone (LHRH) agonist delivering 2 months of therapy before starting radiation and completing treatment with the end of radiation. The second study began radiation concurrently with the LHRH agonist and continued the therapy indefinitely. The median duration of hormone therapy in this group was 24 months. In a recent analysis of the results of these two trials, there appeared to be a small advantage favoring the longer course of therapy, although the results are not conclusive because of slight differences in the eligibility for the two studies. Most of the patients in both studies had T3N0 tumors, but patients with involved lymph nodes, positive margins following radical prostatectomy, and high-grade tumors were eligible for the study with indefinite hormones.

The final study by Bolla et al reported a European randomized trial comparing radiation and 3 years of hormonal therapy to radiation alone. The authors demonstrated a survival benefit with a 5-year overall survival of 79% in the patients receiving radiation and hormones versus 62% in men treated with radiation alone. Most of these men had T3N0 disease based on CT scan, lymphangiogram, or node sampling, although approximately 10% of the patients on each arm had T3 WHO grade 3 tumors. One concern here is that men treated with radiation alone ended treatment within 2 months after registration, whereas the hormone group had 3 years of treatment after registration.

Published literature and current-practice trends generally support the use of androgen deprivation in intermediate- and high-risk patients. Patients with low-risk disease who have especially large prostates may benefit from a short course of androgen deprivation in an attempt at volume reduction. If the gland can be decreased in size to less than 50 to 60 $cm^3$, brachytherapy may be a suitable alternative to external beam in some patients. For patients in the intermediate-risk group, a course of 6 months of androgen deprivation is usually given. Longer courses of androgen deprivation of 2 to 3 years are generally prescribed for patients falling in the high-risk categories. Side effects from androgen deprivation, which include impotence, hot flashes, and anemia, should be discussed with patients before they are placed on long-term androgen deprivation. Furthermore, long-term androgen deprivation has been shown to increase cardiovascular risks, so the duration of hormonal treatments should be specifically tailored to the individual patient.

A number of centers have reported that men in the intermediate-risk group appear to have a longer biochemical disease-free survival with higher doses of radiation and the higher doses may be a substitute for the addition of hormonal therapy. Longer follow-up data are needed to determine whether the difference will translate into a longer overall survival. Hanks initially reported in a retrospective review that the **biochemical no evidence of disease (bNED) survival** was better with doses greater than 76 Gy than with doses less than 70 Gy. Numerous subsequent studies have compared different doses of radiation therapy, and centers continue to **dose escalate** with newer radiation techniques. Treating the prostate to a minimum of 75 Gy has become standard, and some institutions are trying to push the dose to as high as 91 Gy. Whether these higher doses result in better tumor control or improved survival remains to be determined.

Patients who undergo prostatectomy for their prostate cancer must continue to be monitored. Theoretically, PSA levels in these patients should be undetectable. However, for patients with rising PSA after prostatectomy, radiation has been shown to salvage almost 50% of these patients. This scenario should not be confused with adjuvant radiation therapy following prostatectomy. An estimated 25% to 33% of patients who undergo radical surgery will unfortunately have biochemical failures. Retrospective studies have demonstrated that patients with favorable characteristics of PSA doubling time of greater than 10 months, positive margins on pathological review, a Gleason score of 4 to 7, and a presalvage radiation PSA of less than 2 ng/mL had a 4-year progression-free probability of close to 70%; alternatively, the presence of these factors reduced this figure to below 20%.

Patients who are at high risk for local recurrence after prostatectomy should be evaluated for adjuvant radiation. These risk factors include the presence of extracapsular extension, seminal vesicle involvement, and positive surgical margins. Three postoperative phase 3 randomized trials each demonstrated improved biochemical progression-free survival or metastasis-free survival for patients with high-risk features who received radiation in the adjuvant setting. The SWOG92 08794 study, in particular, specifically demonstrated an improvement in overall survival from 49% to 58% at 12.7 years in these high-risk patients who received adjuvant radiation compared to observation after radical prostatectomy. Patients with detectable PSA after prostatectomy should be offered radiation in the salvage setting.

Toxicity from salvage and adjuvant radiation is substantially increased compared to patients treated with radiation alone. Urinary incontinence is often an issue immediately following prostatectomy, and these symptoms usually stabilize after radiation. Therefore it is suggested to wait until incontinence has resolved or achieved maximal improvement before initiating radiation.

## TESTICULAR CANCER

The role of radiation in managing testicular tumors is limited to the management of seminoma. Data show efficacy for radiation in clinical stage I nonseminomatous germ cell tumors, but the necessary dose and the associated toxicity suggest that these patients are better treated with more extensive staging and close observation or chemotherapy if indicated. Radiation should be considered for adjuvant treatment for seminomas because of the unique sensitivity of these germ cell tumors to radiation. Almost all cells need to divide to express the lethal effects of radiation; seminoma cells undergo an intermitotic death because of their inability to accumulate and repair sublethal damage. Because of this characteristic, there is no shoulder on the cell survival curve making them exquisitely radiosensitive.

Staging of seminomas requires chest radiology to rule out metastatic disease, serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin, and abdominal CT scan or lymphangiography. Men who have not completed their family should consider a semen analysis because 10% of newly diagnosed seminoma patients are infertile, and an estimate of fertility is needed to counsel a patient concerning the effects of treatment on fertility. The use of chest CT is limited to patients with disease beyond the testicle because the incidence of distant metastases in patients with stage I disease is small, as evidenced by the less than 5% relapse rate among patients treated with adjuvant radiation.

The treatment of seminoma has evolved over the last 10 years with the reports by Duchesne and Thomas that in patients followed without adjuvant therapy the risk of recurrence is less than 20%. For men willing to undergo close follow-up with CT scanning and chest x-ray every 3 months for 2 years, observation may be an option with the understanding that they may need higher doses of salvage radiation or chemotherapy if they relapse. Because younger men are the largest group with this tumor, preservation of fertility is an issue and many steps are taken to minimize the scattered radiation to the opposite testicle. However, many men elect surveillance and avoid radiation entirely because there is a low but not insignificant risk of developing a secondary malignancy from the radiation treatments.

In an effort to further reduce the dose to the testicle, Fossa et al have reported the results of a randomized trial with treatment to the paraaortic lymph nodes and renal hilum versus the same field plus the common and external iliac nodes. Figure 18-3 shows radiation treatment fields for treatment of the paraaortic lymph nodes. Because most of the scattered dose to the testicle comes from the pelvic portion of the field, eliminating this part of the field substantially reduces the dose to the testicle and the risks of treatment-related infertility. Doses between 24 and 30 Gy are used to treat these tumors because these doses have been shown

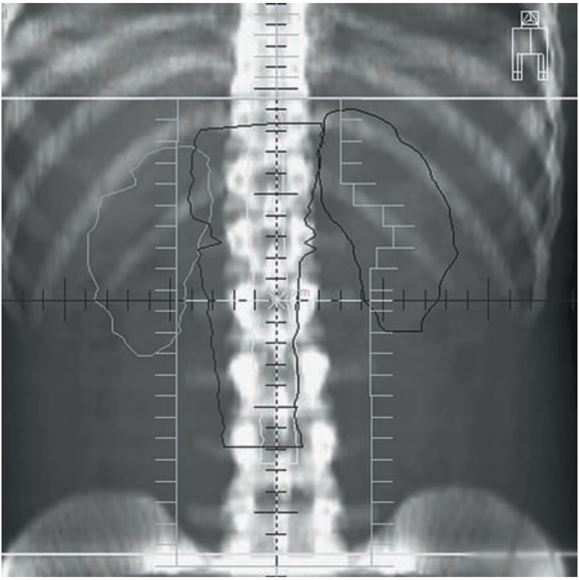

FIGURE 18-3 Radiation treatment fields to treat the paraaortic lymph nodes in patients with seminomas. The left and right kidneys are outlined to block excess dose to these structures.

to reduce the risk of retroperitoneal recurrence from 15% to less than 1% in both groups. The incidence of azospermia was reduced from 30% in the group treated to the iliac region to 11% in the group treated to the paraaortic nodes only. The 11% figure is identical to the risk of primary infertility with no adjuvant therapy in men with a history of seminoma.

Patients with Stage II seminoma tumors are a heterogeneous group including patients with retroperitoneal nodes measuring between 1 and 20 cm. Patients with nodes smaller than 5 cm are generally treated with radiation fields similar to those used to treat a stage I tumor with the inclusion of the external and common iliac nodes. After a dose of 25 to 30 Gy is delivered, the initially involved nodal areas are boosted to a total dose of 35 to 40 Gy. Relapse-free survival rates approach 90%. Some experts argue that this can be further reduced by prophylactic radiation to the mediastinum, although this is a matter of institutional policy and has not been studied in a prospective trial.

Acute and long-term toxicity is the limiting factor with radiation therapy. Abdominal radiation to a dose of 40 Gy will cause some scarring, increasing the risk of peptic ulcer, and complicating any future surgery that might be necessary in these relatively young men. There are also reports of an increased risk of Raynaud phenomena and a possible increased risk of cerebrovascular disease in men treated with cisplatin, vinblastine, and bleomycin. It would appear that neither treatment offers a survival or disease-free survival benefit and therefore treatment should be individualized. There is little modern experience with radiation for stage III and IV seminoma, and the results that are available suggest that these patients are better treated with chemotherapy. It should be noted that a history of seminoma in one testicle puts the patient at risk for seminoma in the other testicle and these patients should be carefully monitored for their lifetime.

## PENILE CANCER

Squamous cell carcinoma of the penis is rare in the United States and is more prevalent in other countries. Most patients are treated with initial surgery, but some patients are not candidates for surgery or refuse surgery. Superficial lesions can be treated with either external radiation or interstitial radiation using radium needles or iridium seeds in catheters. It is frequently necessary to treat the superficial inguinal nodes because 50% of men will have palpable adenopathy and the risk of occult involvement of nodes is high in men with poorly differentiated tumors or tumors of the glans. If a patient is treated with external radiation, he may most easily be treated with an en face electron beam to treat the penis and the lymph nodes (which can lie at a depth of 5 cm below the skin). However, this beam arrangement results in significant toxicity, and with CT planning, IMRT is more likely to be used. A dose of 45 to 50 Gy is generally prescribed to treat clinically uninvolved skin and lymph nodes, but the primary tumor and areas of gross disease need to be treated to a dose of 65 to 70 Gy. Morbidity of radiation to this area includes moist desquamation of the penis and scrotum with accompanying edema, often lasting 8 to 12 weeks after radiation. Nodal dissection increases the frequency and severity of edema. For small, low-grade tumors (less than 2 cm) of the shaft of the penis, the risk of nodal involvement is low, and these patients may be treated with interstitial radiation to the local area only.

Most of the series of definitive radiation are small; as a group, they suggest that radiation is effective in controlling the tumor, but the morbidity is substantial. Haile and Delclos reported that in eight patients treated with external radiation, seven were controlled, but one patient required surgical amputation because of necrosis, whereas 11 of 12 patients treated with brachytherapy were controlled, with one patient requiring amputation for necrosis. In older series, Knudsen and Brennhovd and Lederman described a lower control rate (38% and 30%, respectively), and 6% of the patients required amputation of the penis for necrosis. Duncan and Jackson reported the experience of the Holt Radium Institute initially with brachytherapy and subsequently with external beam radiation. They found that the control rates improved from 46% to 90% with external beam radiation because of the ability to treat larger volumes with a more homogenous dose and adequately cover the tumor. At the same time, these authors found that the risk of urethral stricture or penile necrosis rose from 4% to 10%. Although radiation may be used to treat this disease, significant morbidity and the treatment requires a commitment on the part of the patient and physician to persist in treatment despite the acute toxicity. It remains to be determined whether radiation and chemotherapy may be combined to reduce the risk of distant metastases and to allow lower doses of radiation to be used to minimize the morbidity.

## Summary

Extensive experience with radiation in the treatment of genitourinary tumors demonstrates that it is an effective adjuvant treatment for selected patients. External and interstitial radiation, possibly with hormones, may be an effective alternative to radical prostatectomy for prostate cancer or to penectomy for penile cancers. Radiation with chemotherapy may be an alternative to radical cystectomy in bladder cancer patients with comorbid medical conditions or extensive nonmetastatic tumors that preclude surgery.

Treatment decisions must be individualized based on the clinical findings and patient preferences. Although the incidence of incontinence following radical prostatectomy may vary from 1% to 30%, the incidence of both local and proctitis following radiation may vary from 3% to 20% following radiation. In facilities with state-of-the-art equipment and physicians with specialized skills, there may be little to recommend one treatment over another, whereas in other facilities, one department may have special abilities that would suggest that there may be a treatment preference based on the institutional experience.

It is likewise necessary to consider the working relationship between the departments of urology and radiation oncology within each institution. Even though chemosensitized radiation may be equivalent to radical cystectomy, it may not be desirable to pursue a course of bladder conservation if the urologist does not believe that a salvage cystectomy is possible after radiation.

Because there may be alternatives that are similarly effective, it is important to avoid confusing patients with conflicting claims of superior results. Patients should be presented with all alternatives for treatment and select the treatment that will produce the most desirable results and the most acceptable morbidity risks. The current directions of radiation research include exploring combinations of hormones and radiation and higher doses of radiation in the management of prostate cancer.

## CLINICAL PEARLS

1. Radiation doses above 76 Gy can be safely prescribed to the prostate and seminal vesicles without significant toxicity using modern radiation technologies.
2. Patients with rising PSA after radical prostatectomy should be referred for salvage irradiation therapy.
3. Patients who are not surgical candidates for treatment of bladder cancer should be offered definitive chemoradiation as an alternative cystectomy.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What factors need to be assessed in deciding treatment options for patients with prostate cancer?*
2. *Compare and contrast the risks and benefits of prostate brachytherapy and external beam radiation for the management of prostate cancer. What are the benefits of protons for the treatment of prostate cancer?*
3. *Which groups of patients would benefit from androgen deprivation therapy in management of prostate cancer?*
4. *What are possible options for a patient who does not want to undergo cystectomy for management of bladder cancer?*
5. *What are the risks and benefits of irradiation for patients with seminoma?*

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## CHAPTER 19

# Laparoscopic Surgical Anatomy, Laparoscopy, and Robotic-Assisted Laparoscopic Surgery

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## Introduction

Minimally invasive surgery via a laparoscopic or robotic-assisted approach has become the gold standard for many urologic procedures. While providing equivalent efficacy in a number of upper and lower urinary tract surgeries, laparoscopic procedures have a distinct advantage over open techniques in postoperative pain, cosmesis, recovery, and length of stay. A thorough knowledge of the basics of laparoscopy and laparoscopic anatomy is essential for any practicing urologic surgeon.

## Patient Selection

**A minimally invasive approach is considered the standard of care for radical nephrectomy for T1-T3a renal cell carcinoma, adrenalectomy for benign pathology, simple nephrectomy for benign disease, nephroureterectomy for urothelial carcinoma, dismembered pyeloplasty in adults, and pelvic lymphadenectomy.** Urologic surgeries for which a laparoscopic technique is an acceptable alternative standard of care include partial nephrectomy, radical prostatectomy, and living-donor nephrectomy.

In choosing patients for laparoscopic surgery, absolute and relative contraindications must be considered. **Absolute contraindications to laparoscopic surgery are no different than for open alternatives** (i.e., uncorrected coagulopathy, severe performance status/cardiopulmonary disease). There are a number of relative contraindications to laparoscopic surgery. However, all patients with a relative contraindication are amenable to laparoscopic surgery under certain circumstances.

## RELATIVE CONTRAINDICATIONS

COPD: Typically, the abdomen is insufflated using carbon dioxide ($CO_2$). Those with chronic obstructive pulmonary disease (COPD) are at danger of developing hypercarbia secondary to $CO_2$ reabsorption after insufflation, but may benefit postoperatively from reduced narcotic requirements and improved pulmonary toilet. In patients with normal pulmonary function, this $CO_2$ is easily removed from the body by the lungs. However, the lungs ability to do so in COPD is impaired, resulting in hypercarbia. Methods to decrease the $CO_2$ reabsorption in those with COPD include changing the insufflation gas to helium and lowering intraabdominal insufflation pressure to 10-12 mm Hg.

Pregnancy: This was previously believed to be a relative contraindication to laparoscopic surgery but now is not. Concerns were raised in regard to placental ischemia induced by pneumoperitoneum. These concerns were not corroborated in animal studies. In animal models, intraabdominal pressure (IAP) up to 10 mm Hg was considered safe; however, increasing the working pressure to 20 mm Hg produced maternal and fetal cardiopulmonary compromise. In fact, laparoscopic cholecystectomy and appendectomy are considered the standard of care during pregnancy.

Obesity: Obesity was previously believed to be a relative contraindication to laparoscopic urologic surgery, but is no longer. In fact, the postoperative morbidity decrease from laparoscopic surgery is greater in the obese population as compared with the normal population. It has been shown, in upper urinary tract laparoscopic surgery, that patients with BMI greater than 30 kg/m$^2$ had higher operative time, blood loss, and transfusion rates as compared with lean counterparts. However, major and minor complications were no different in the obese population. Conversion rates and analgesic requirements were also no different in lean versus obese patients.

Previous abdominal surgery: Intraabdominal adhesions were previously thought to be a contraindication to laparoscopic surgery but are no longer. There are circumstances in which a laparoscopic lysis of adhesions (LOA) should not be undertaken, including peritonitis, hemodynamic instability, and coagulopathy. However, in the overwhelming majority of patients, laparoscopic LOA can be done with efficiency and safety, provided the surgeon is familiar with the technique. In fact, laparoscopic LOA has been shown to confer a quicker recovery of bowel function and fewer wound complications as compared with open LOA. Minimally invasive retroperitoneal approaches can also be utilized to avoid the potential adhesions seen after previous intraabdominal surgery.

# Patient Positioning

## RENAL SURGERY

### Transperitoneal Approach

The patient is positioned in a 60- to 90-degree flank position with the operative side up. Decompression of the bowels and bladder via a nasogastric/orogastric tube and Foley catheter should be done prior to prepping the patient. The patient should be carefully padded at all pressure points, and an axillary roll should be placed to prevent brachial plexus injury.

In regard to positioning on the bed, the break should lie between the twelfth rib and the anterior superior iliac spine once the patient is in flank position. The table should be flexed slightly, and the anesthesia team should properly bolster the patient's head so it is not flexed downward. The lower leg should be flexed at the knee, and the upper leg should be straight. The patient may be secured to the bed using straps or tape. A "test roll" should be performed with operative personnel on both sides of the bed to ensure that the patient is properly secured. An arm board is placed on the side of the bed to which the patient is facing, and the arm should be placed palm down in a natural position with no tension. Once the above position is attained, the patient may be prepped (Figure 19-1).

### Retroperitoneal Approach

Retroperitoneal renal surgery requires the patient to be placed in a full flank position, and the table should be flexed as much as possible to facilitate retroperitoneal dissection. The patient's ventral surface should be more towards the midline, rather than the edge, of the bed.

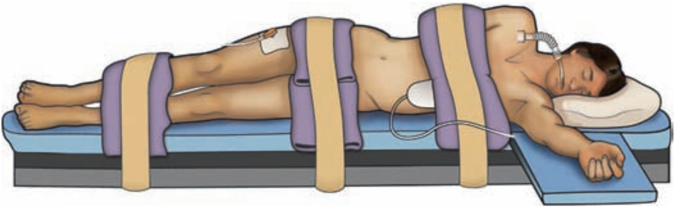

**FIGURE 19-1 Positioning for renal surgery.** (From Kavoussi LR, Schwartz MJ, Inderbir SG: Laparoscopic surgery of the kidney. In Wein AJ, Kavoussi L, Novick A, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

## Robotic-Assisted Laparoscopic Prostatectomy

This description will focus on robot-assisted laparoscopic prostatectomy (RALP). Positioning for laparoscopic prostatectomy is similar.

The patient should be placed in a low lithotomy position to allow for the robot to be positioned between the patient's lower extremities. Alternatively, split leg positioners may be used. **The patient is placed in extreme Trendelenburg, allowing gravity to retract intraabdominal contents cranially.** The patient's buttocks should be brought to the end of the table, and the weight of the leg should be on the patient's heel, which should be padded. The arms should be placed on either side and tucked, with the palms oriented so the thumbs are anterior. The elbows should be padded, and a strap should be placed over the patient's chest. The strap should be placed so that a hand can be put between the strap and the patient's body, but no tighter, to allow for adequate chest wall excursion. A Foley catheter should be placed after the patient is prepped, and a nasogastric/orogastric tube should be placed prior to prepping.

## Other Pelvic and Upper Tract Surgery

Other laparoscopic urologic surgery positioning may be adapted from the above. For instance, robot-assisted and pure laparoscopic cystectomy or ureterectomy and reimplantation can be done from the same positioning as RALP, and robot-assisted and pure laparoscopic upper urinary tract surgery can be done from the same positioning as laparoscopic renal surgery (i.e., pyeloplasty can be done from the same positioning as transperitoneal laparoscopic renal surgery).

## Access

Obtaining access to the peritoneal cavity is done primarily via two techniques (Veress [closed] or Hasson [open]) techniques. Each technique will be described in detail and both are safe and effective means of accessing and insufflating the peritoneal activity. The surgeon should choose the technique with which he or she is most comfortable.

### CLOSED (VERESS) ACCESS

The Veress needle has a spring-loaded inner sheath. When the needle engages tissue, this sheath retracts, allowing the needle to puncture the tissue. Once the needle passes into the peritoneal cavity, the sheath deploys and guards the needle tip which greatly decreases the likelihood of injury to intraabdominal vessels and viscera.

Safe access to the peritoneal space via the Veress technique is accomplished by employing the technique correctly. Three “clicks” are heard when the needle passes through the following layers on the anterior abdominal wall: skin, anterior rectus sheath, and posterior rectus sheath. Once the third “click” is heard, the needle should be held in this position. Rotating the needle could cause intraabdominal injuries if the needle is in the wrong position. The needle should then be aspirated, and the contents of aspiration should be examined. Succus or blood indicates the needle is in bowel or vasculature, respectively. If this is the case, the needle should not be removed. Instead, an alternate Veress needle puncture site should be chosen and the above technique repeated. After the initial aspiration, 2 cc of saline should be irrigated, and aspiration should be repeated. The needle should aspirate easily. The saline should quickly drop into the peritoneal space, provided the needle is in the correct location.

The needle can then be connected to high-flow insufflation. The caliber of the Veress needle limits the inflow to no greater than 3 L/min. Attention should be paid to the pressure transduced, which should be less than 10 mm Hg. There are a number of reasons why the initial insufflation pressure may initially read greater than 10 mm Hg. If the needle is abutting an intraabdominal viscus, pressure may be elevated. In this circumstance, pressure may be reduced by retracting the abdominal pannus up, away from this viscus. In very obese patients, the weight of the abdominal wall may cause increased initial pressures, which will decrease with continued insufflation. If the abdomen is not uniformly insufflated, and the pressure persists greater than 10 mm Hg, the needle is in the preperitoneal space and needs to be advanced.

The primary trocar can then be advanced via a blind or optical trocar (nonbladed). The laparoscope is then introduced to survey the abdomen for anatomic variation, adhesions, and damage to viscera or vessels from the Veress needle or initial trocar. Remaining trocars can then be placed under direct visualization. The Veress needle is removed, and the insufflation tubing is connected to the camera trocar.

### HASSON (OPEN) ACCESS

The first step in this technique is accessing the peritoneal space via a 12-mm or smaller incision. A Hasson or balloon trocar can be used. The trocar can be affixed to the fascia to ensure that it is not dislodged during the procedure. Insufflation is then connected to this trocar, and the abdomen can be surveyed. The sutures used to affix the trocar to the fascia can be used at the conclusion of the procedure to close the fascial defect.

The Hasson technique should be used in children and pregnant patients. It should also be noted that current literature does not support the closed or the open technique as safer relative to the other.

## Physiologic Changes of Pneumoperitoneum

Pneumoperitoneum is traditionally attained using $CO_2$ gas maintained at an IAP of 15 mm Hg. **Animal studies have shown that increasing IAP to 20 mm Hg can result in impaired renal, cardiac, and pulmonary function**. However, it should be noted that brief increases in IAP to 20 mm Hg appear to not be physiologically deleterious. In animal studies, impaired cardiac and pulmonary function at 20 mm Hg IAP was seen after 3 hours.

## CARDIOVASCULAR EFFECTS

**The overall effect of pneumoperitoneum produces no change in cardiac output.** Pneumoperitoneum compresses the vasculature, increasing peripheral arterial resistance and central venous pressure. Increased central venous pressure leads to decreased peripheral venous return. The heart rate increases in response to decreased preload, and cardiac output remains the same. However, arrhythmias are more common with pneumoperitoneum. $CO_2$ induces hypercarbia and acidosis and increases the sympathetic response, all of which contribute to an increased incidence of arrhythmias.

## PULMONARY EFFECTS

Pneumoperitoneum increases IAP. This increase in IAP is transmitted to the thoracic cavity. The result of the increased thoracic cavity pressure is decreased compliance, thereby increasing peak and mean airway pressures. Also, vital capacity is reduced. $CO_2$ diffuses into the thoracic cavity, causing hypercarbia and acidosis. Hypercarbia induced by $CO_2$ is usually inconsequential in those with normal pulmonary function. However, as mentioned previously, those with COPD may have difficulty eliminating this excess $CO_2$. As such, arterial blood gases may be used to measure arterial $CO_2$ saturations in this patient population. If hypercarbia develops, decreasing the IAP to 10 mm Hg and/or changing the insufflation gas to helium can reduce this effect.

Many robot-assisted pelvic surgeries are done with the patient positioned in steep Trendelenburg. **Trendelenburg positioning reduces chest wall compliance, impairing $O_2$ exchange. In this situation, compliance can be improved by increasing respiratory rate and tidal volume.**

## RENAL EFFECTS

**Decreased urine output results from pneumoperitoneum caused by decreased renal blood flow and renal parenchyma compression.** This decreased urine output returns to normal once the abdomen is desufflated. The anesthesia team should be cognizant that urine output will return to normal postoperatively so the patient is not overhydrated prior to or during the procedure.

## Trocar Placement

Stylistic differences exist among laparoscopic surgeons in regard to trocar placement. We provide a description for effective trocar placement that can be adapted per surgeon preference and patient anatomic differences.

The camera can be placed via the initial access trocar or through a secondary trocar, depending on the procedure to be performed and the location of initial trocar placement. In general, the camera should face the same direction as the surgeon's instruments so the surgeon does not have to mentally reverse the laparoscopic image. Trocars should be placed in a position that the surgeon finds ergonomically acceptable, and should be placed 7 to 10 cm away from one another to prevent arm clashing. **During robotic surgery, a minimal distance of 8 cm is needed between robotic arms in order to limit intraoperative collisions.**

### TRANSPERITONEAL RENAL SURGERY

The initial trocar placement (5 or 12 mm) is halfway between the anterior superior iliac spine (ASIS) and umbilicus, just lateral to the rectus muscle. For obese patients, the umbilicus is a less useful landmark, and ports must be moved laterally. A second trocar (5 or 12 mm, dilating) is placed in line with the first trocar, but approximately 2 to 3 fingerbreadths below the costal margin. Trocars may need to be adjusted, depending on patient body habitus. The third trocar (5 or 12 mm) is placed in the midline, just lateral to the umbilicus, midway between the first and second trocars. The third trocar is the camera port. Additional trocars can be placed as seen fit. Often a fourth trocar is placed more laterally than the most inferior trocar and used to help retract the kidney. For right-sided renal surgeries, a 5-mm trocar can be placed immediately below the xiphoid process to accommodate a self-retaining retractor to retract the liver cranially (Figure 19-2).

### RETROPERITONEAL RENAL SURGERY

While transperitoneal renal surgery access can be attained via an open or closed technique, retroperitoneal renal surgery access is uniformly performed via an open technique. After positioning as previously described, a 2-cm incision is made off the tip of the twelfth rib, and the retroperitoneal space is accessed by a combination of sharp and blunt dissection. The lower pole of the kidney

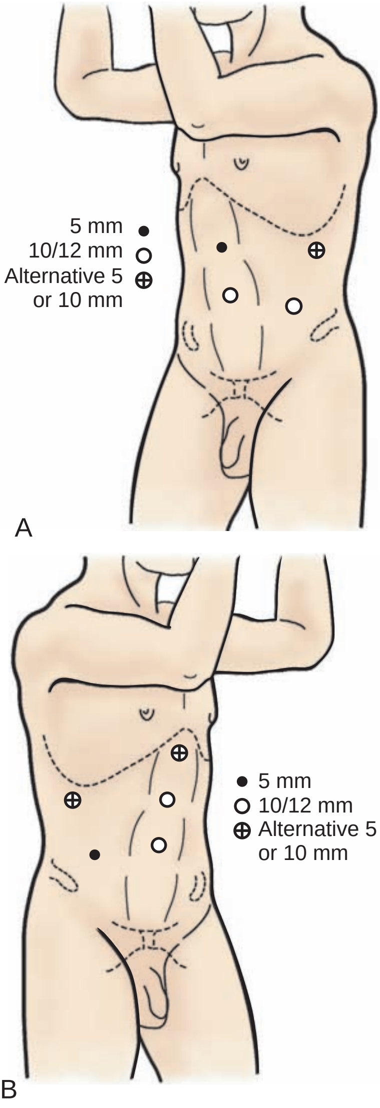

**FIGURE 19-2 Port placement for transperitoneal renal surgery.** (From Kavoussi LR, Schwartz MJ, Inderbir SG. Laparoscopic surgery of the kidney. In Wein AJ, Kavoussi L, Novick A, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

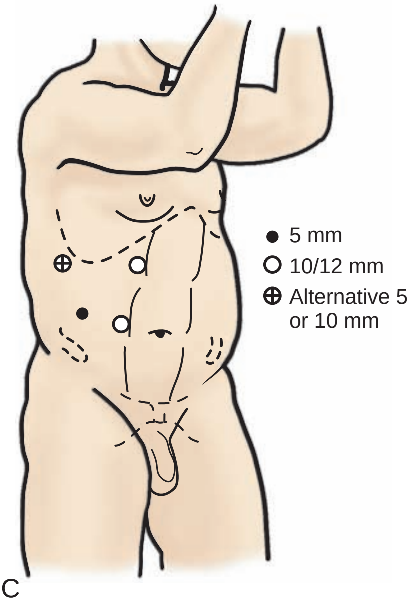

FIGURE 19-2, cont'd

can be palpated, and retroperitoneal fat is visualized. A balloon dilator is used to expand the retroperitoneal space to approximately 800 cc. A secondary trocar is typically placed lateral to the paraspinous muscle at the costovertebral angle. Via this trocar, the peritoneum is swept forward to allow space for the third trocar to be placed. The third trocar is placed anteriorly to the primary access site along the same line as the first two trocars (Figure 19-3). Adjustments for obesity are not necessary during retroperitoneal surgery.

## HAND-ASSISTED LAPAROSCOPIC RENAL SURGERY

Access may be attained via an open (Hasson) or closed (Veress) technique. Alternatively, the hand port itself can be used to insufflate the abdomen. The hand port is usually placed in a periumbilical location, and the incision is made commiserate with the surgeon's glove size (i.e., a size 7 glove should make a 7-cm

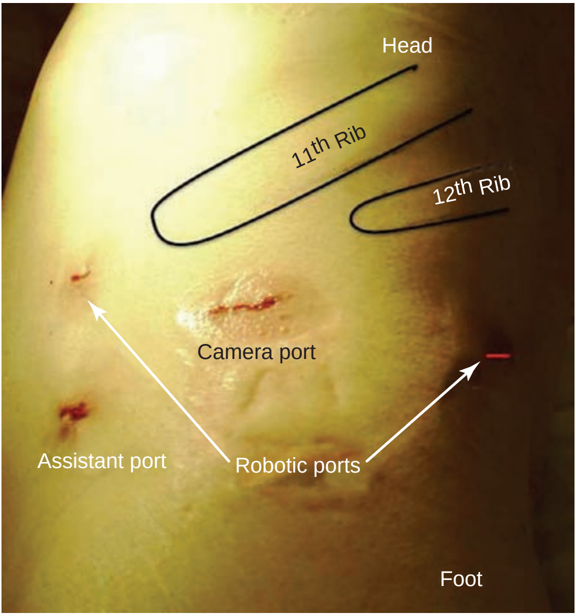

FIGURE 19-3 Port placement for retroperitoneal renal surgery.

initial incision). Additional trocars can then be placed under direct vision or using the surgeon's hand to safely guide the trocar into position.

## PROSTATECTOMY

Pure laparoscopic prostatectomy has comparable port location to the robotic approach. For robotic prostatectomy, adaptations of the following configuration are typically used. Three robotic arms are classically used, with one 12-mm camera trocar and two assistant ports. The assistant ports may be placed on the right or left sides, depending on surgeon preference. The symphysis pubis is marked after insufflation, and the camera port is placed one fingerbreadth above the umbilicus. The camera port is the primary access trocar (12 mm). The #1 and #3 robotic arms are placed on the patient’s right side, at least 7 cm apart but usually 8 cm apart. The #1 arm is no closer than 14 cm to the superior aspect of the symphysis pubis. On the left, the #2 is placed in a

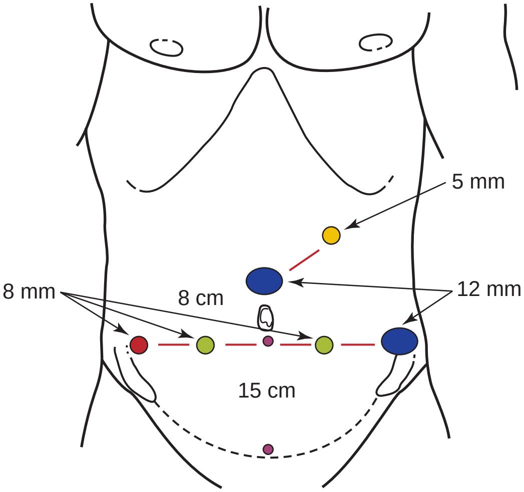

FIGURE 19-4 Port placement for robotic-assisted laparoscopic prostatectomy.

mirrored position as the #1 arm and the assistant port (12 mm, dilating trocar) is placed 7 cm lateral to the #2 arm. The second assistant port (5 mm) is placed at a 45-degree angle cranial and lateral to the camera port (Figure 19-4).

### OTHER UPPER TRACT AND PELVIC SURGERIES

Port placement for other upper urinary tract procedures and pelvic surgery may be adapted from the above port descriptions for renal and prostate surgery.

## Surgical Anatomy of the Upper Urinary Tract

The kidney and upper urinary tract can be dissected laparoscopically via a transperitoneal or retroperitoneal approach. Anatomy differs whether working on the right or left side. On the right, the liver will immediately come into view and typically drapes over the upper pole of the kidney. The right or left colon should immediately be identified to establish its course in preparation of incision of the white line of Toldt membrane (Figure 19-5). Once the colon is reflected medially, mesenteric fat be can be

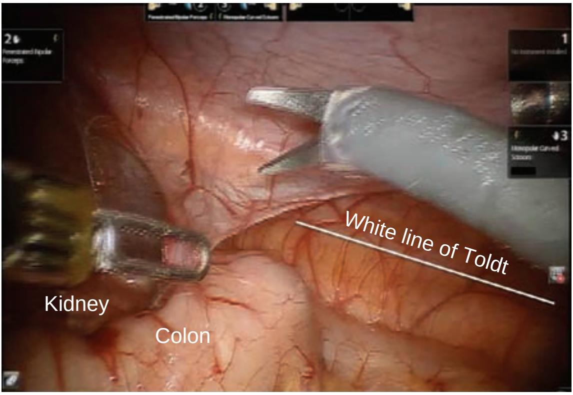

FIGURE 19-5 Incision of the white line of Toldt membrane.

swept medially. It is important for the surgeon to be cognizant of the differing appearance of retroperitoneal/perirenal fat as compared with mesenteric fat to properly create this plane of dissection. Staying directly on top of Gerota fascia between the perirenal and mesenteric fat creates an avascular dissection and bloodless field. Once the colon is adequately reflected, and the mesenteric fat is swept medially, the psoas muscle will come into view posterior and inferior to the kidney. Overlying the psoas muscle will be the genitofemoral nerve and psoas tendon. The gonadal vein and ureter are identified medial to the psoas muscle and kidney (Figure 19-6). The gonadal vein is often encountered first during a transperitoneal dissection, and the ureter is found just medial and below the gonadal vein at the lower pole of the kidney. Subsequently, the ureter and gonadal vein can be traced cranially and used as a road map to the renal hilum.

In the region of the kidney itself, the colon must be medially rotated to expose the renal hilum. **Once the colon is reflected medially, the first significant structure that is noted on the medial surface of the kidney is the duodenum. This must be Kocherized to gain access to the hilum.** The next major structure encountered, oriented on a horizontal plane, is the inferior vena cava (IVC). Careful dissection along the IVC reveals the insertion of the gonadal vein, the main renal vein, and the adrenal vein from caudal to cranial. Most commonly, the renal artery lies directly

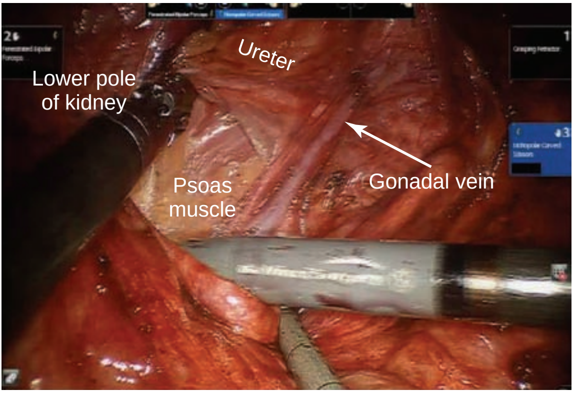

FIGURE 19-6 Gonadal vein and ureter on the left side.

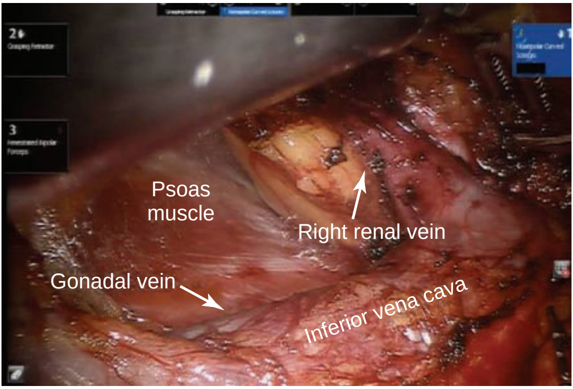

FIGURE 19-7 Right renal venous anatomy.

superior and posterior to the renal vein (Figure 19-7). Often the ureter can be mobilized and used to lift the kidney upward; this upward retraction can facilitate hilar dissection. Once the main hilar structures have been divided, access can then be obtained to the adrenal gland that will lie just medial to the upper pole of the kidney (Figure 19-8). **The adrenal vein drains directly into the vena cava and must be clearly identified if the adrenal gland is to be resected. Due to its short size and direct drainage into the IVC,**

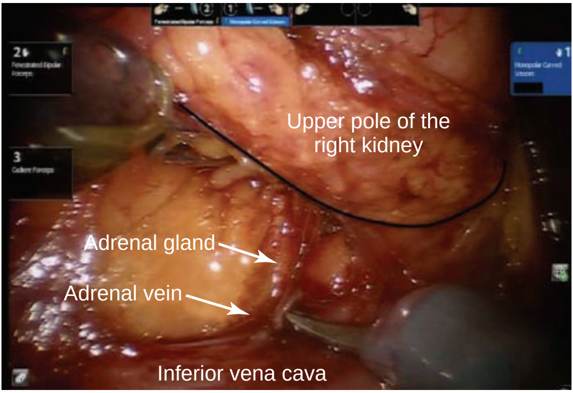

FIGURE 19-8 Adrenal vein on the right side.

**the right-sided adrenal vein is sometimes called the *vein of death* because significant bleeding can be encountered if the vein is torn during the dissection.**

On the left side, the spleen lies anterior and superior to the kidney. There is a very consistent adhesion (splenocolic ligaments) from the left colon to the side wall just inferior to the spleen. This is usually the point at which the left colon mobilization is begun. After the colon is reflected medially in a similar fashion as the right side, the same landmarks are identified. However, the left gonadal vein can be much more useful as compared with the right, and dissection along this structure leads directly to the left renal vein. Releasing the splenorenal ligaments also aids in allowing the spleen and colon to reflect medially, which can aid in the hilar dissection. Care must be taken to avoid injuring the stomach during this part of the dissection. Attention must also be made to avoid injury to the tail of the pancreas or splenic vein during the dissection of the medial surface of the upper pole of the left kidney.

On the left, the aorta will be the dominant structure crossing horizontally across the bottom of the dissection field. **As the hilum is approached along the course of the gonadal vein, it is also important to remember the venous tributaries of the left renal vein. The adrenal vein, the ascending lumbar vein, and the gonadal vein all consistently drain into the renal vein** (Figure 19-9).

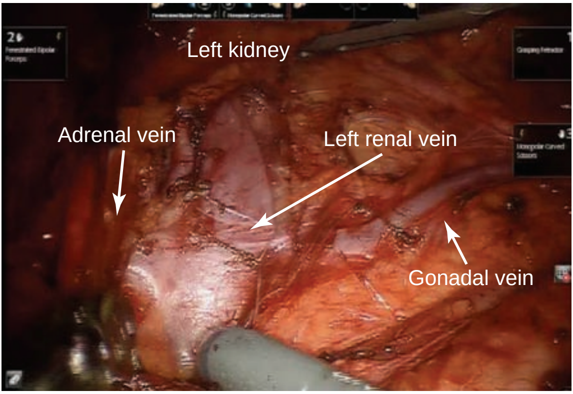

FIGURE 19-9 Left renal venous anatomy.

If an adrenalectomy alone is targeted, then the adrenal vein is ligated and the adrenal can be easily dissected off the anteromedial surface of the kidney.

As on the right side, the left renal artery is usually directly behind the renal vein. Arterial supply to the adrenal gland on the right and the left side is derived from three sources: the inferior phrenic artery, directly from the aorta, and the ipsilateral renal artery.

Laparoscopic retroperitoneal renal surgery can be challenging because of a lack of working space and unfamiliarity of the laparoscopic landscape in the retroperitoneum. Care must be taken to maintain the proper anatomic landmarks during the dissection in order to avoid catastrophic mistakes. The approach is similar on the left and right side. If the proper space is made by inflating an expansion balloon directly on the psoas muscle, the kidney, encased in Gerota fascia, will remain attached to the anterior abdominal wall and be "above" the surgeon throughout most of the case. The psoas muscle must always be in an inferior and horizontal position on the laparoscopic screen. **Once the retroperitoneal space is developed, an incision 2 cm above the psoas muscle into Gerota fascia is made.** If the dissection is carried too close to the psoas muscle, it can be carried directly under the great vessels, which can lead to injuries to the contralateral kidney. Dissection in the plane 2 cm above and parallel to the psoas muscle should lead to the renal artery. Pulsations in the perirenal fat can help guide the dissection. Since the camera port is placed almost at the level of the hilum, the renal vessels should be directly in front of the surgeon. The renal vein will lie directly behind the artery in this approach.

## Surgical Anatomy of the Lower Urinary Tract

**In approaching the pelvis laparoscopically, most often the patient will be placed in a supine position and then converted to a Trendelenburg position to allow gravity to retract the bowels into the upper abdomen.** The usual landmarks initially identified for orientation are the medial umbilical ligaments and the internal inguinal rings (Figure 19-10). Posteriorly, the rectum can be seen diving caudally, and the rectovesical pouch is visualized just posterior to the tip of the Foley balloon, anterior to the rectum.

During radical prostatectomy, the bladder can be dropped by incising the peritoneum across both medial umbilical ligaments. This provides access to the space of Retzius, which can be further widened by blunt dissection. Careful dissection distally uncovers the arch of the pubis (Figure 19-11). Superficial fat overlying the prostate and bladder can be mobilized to visualize the endopelvic fascia laterally and puboprostatic ligaments. The superficial complex of the prostate can be seen in the midline of the prostate and is usually small and easily controlled with bipolar electrocautery. The dorsal venous complex is also located at the midline below the prostatic fat and extending into the prostatic capsule.

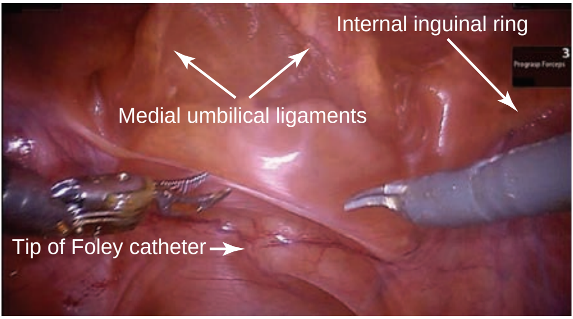

FIGURE 19-10 Initial image for robotic prostatectomy.

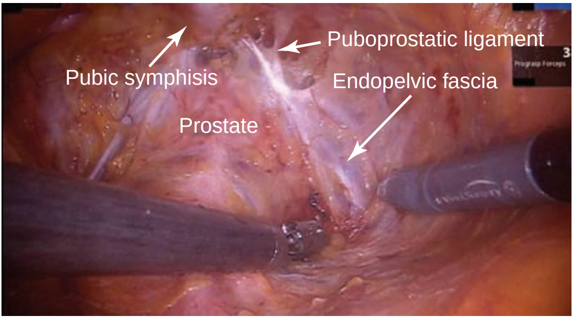

FIGURE 19-11 Endopelvic fascia.

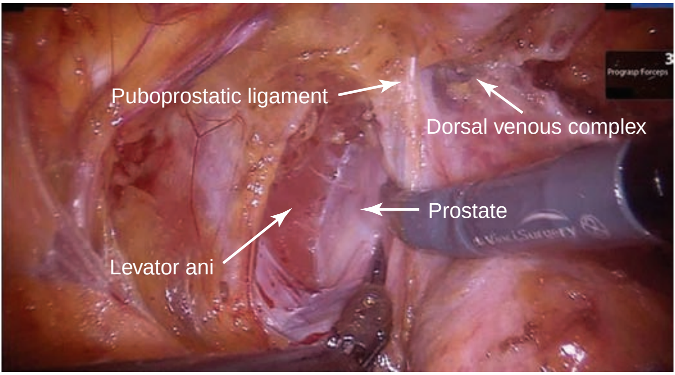

FIGURE 19-12 Incision of endopelvic fascia.

During radical prostatectomy or cystoprostatectomy, the endopelvic fascia is incised from the base of the prostate to the puboprostatic ligaments. The levator muscles are then visualized and gently dissected from the lateral surfaces of the prostate (Figure 19-12). Very fine muscle fibers (Myer's Muscles) can be dissected off the lateral surfaces of the apex of the prostate and lateral edges of the dorsal venous complex. These muscle fibers are very prone to bleeding. The puboprostatic ligaments are then sharply divided. The dorsal venous complex is ligated, either using a suture ligature or a laparoscopic stapler.

Visualization of the vesicoprostatic junction is facilitated by removing periprostatic fat. Identifying the bladder neck can be

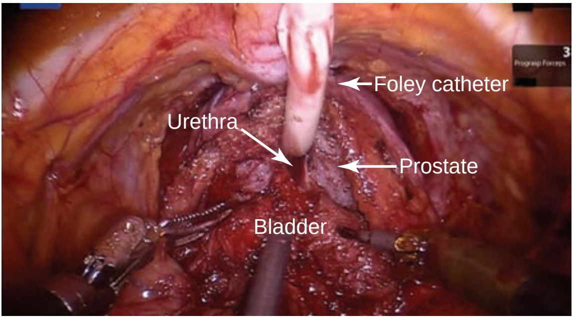

FIGURE 19-13 Dissection of bladder neck and prostate.

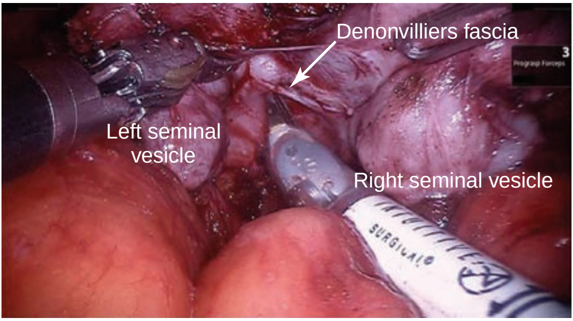

FIGURE 19-14 Denonvilliers fascia.

further facilitated by advancing and retracting the Foley catheter and marking the junction with electrocautery (Figure 19-13). Dissection in the proper plane delineates a clear junction between the smooth prostate capsule and detrusor fibers. Cognizance of detrusor thickness helps the surgeon maintain the correct thickness posteriorly. As the posterior bladder neck is transected, whitish longitudinal fibers can be thinned from a lateral to medial direction, exposing the vasa/seminal vesicles. Once these structures are dissected, Denonvilliers fascia is identified and incised (Figure 19-14). The space between the rectum and prostate can then be developed. If this plane is taken posteriorly and towards the apex of the prostate, only the prostatic pedicles will be left attaching the prostate laterally.

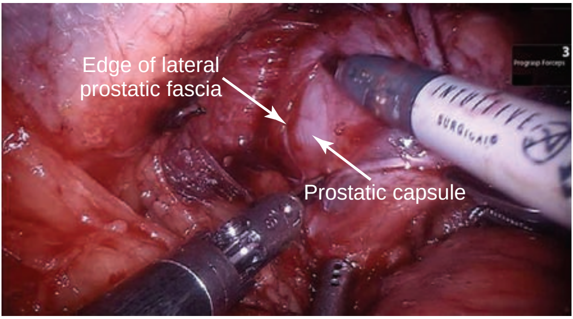

FIGURE 19-15 Release of neurovascular bundle.

Alternatively, during radical prostatectomy, some clinicians prefer to first incise in the anterior rectovesical pouch and perform the vasa/seminal vesicle dissection. During a radical cystoprostatectomy, ligation of the major branches of the internal iliac artery (superior vesicle artery and posterior pedicle of the bladder) and complete division of the peritoneum along the inferior peritoneal fold of the rectovesical pouch allow posterior dissection of the bladder and even the prostate away from the rectum.

**The neurovascular bundles of the prostate run along the posterior-lateral aspects of the prostate and laterally to the prostatic pedicles.** They can be released from the prostate by incising the lateral prostatic fascia and developing a plane of dissection between the neurovascular bundle (which often appears yellow/red) and prostatic capsule (Figure 19-15). This is important during a nerve-sparing radical prostatectomy or cystoprostatectomy.

The apex of the prostate is contiguous with the striated urethral sphincter. The urethra can often be seen after incising the dorsal venous complex as longitudinal muscle fibers extending into the prostate (Figure 19-16).

## Complications

Complications during laparoscopic surgery have been said to be as high as 16%. Most lethal injuries involve trocar placement and are secondary to bowel or major blood vessel injury. We describe the most common complications of laparoscopic surgery and techniques that may prevent their occurrence.

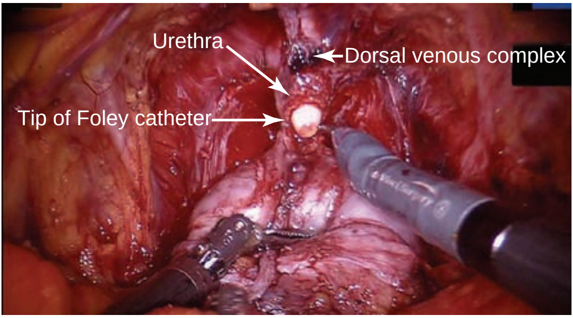

FIGURE 19-16 Dissection of apex of the prostate.

## NEUROMUSCULAR INJURIES

Neuromuscular injuries can largely be prevented preoperatively during patient setup. **Padding all pressure points, properly positioning patients (previously described), and limiting operative time to less than 5 hours are measures that can help prevent these injuries.**

An axillary roll should always be placed during renal surgery to prevent brachial plexus injuries. Bed flexion should be done no more than what is necessary to open up the operative field. Exaggerated flexion has been correlated to a higher incidence of neuromuscular injuries.

Lower leg compartment syndrome is possible when patients are placed in the lithotomy position for an extended amount of time. Lowering the legs every 2 hours can obviate this complication. Padding the lateral surface of the leg and confirming that the weight of the leg lies on the heel prevents peroneal nerve injuries.

**Rhabdomyolysis can occur with patients in the flank or lithotomy position, especially with prolonged operative times.** This complication is more common in males and those with increased body weight. Urine may be tea-colored, and a urine dipstick will be positive for blood but negative for red blood cells. Rhabdomyolysis causes acute renal failure, which is treated with hydration and alkalinization.

## VASCULAR INJURIES

Major vascular injuries account for over 80% of the deaths associated with laparoscopy and usually occur when obtaining access. Proper Veress technique and primary trocar placement can reduce the incidence of vascular injury. If blood is aspirated after Veress needle placement, the needle should not be removed. Instead, a second Veress should be placed elsewhere with the intention of evaluating the location of the first Veress placement. Likewise, if blood fills a trocar during initial placement, the trocar should not be removed. Laparotomy should be undertaken to repair the vascular injury. Repair should not be attempted laparoscopically.

More commonly, nonmajor vessels are injured during laparoscopic surgery. For instance, epigastric vessels may be injured during trocar placement, and this can be prevented by placing a trocar at least 6 cm from the midline or directly in the midline.

## $CO_2$ EMBOLISM

$CO_2$ embolism can occur at any time during laparoscopic surgery. **The hallmarks of $CO_2$ embolism are cardiac collapse, cyanosis of the upper extremities, elevated central venous pressure** (CVP), **and a "millwheel" heart murmur.** Insufflation should be stopped, and the patient should be placed in the left lateral decubitus position. As mentioned previously, if blood is aspirated on initial Veress placement, insufflation should not be performed to prevent $CO_2$ embolism.

## BOWEL INJURIES

It is important to realize that at least half of all bowel injuries are caused by electrocautery, and approximately two thirds are not recognized intraoperatively. **As such, it is essential to be aware of the signs and symptoms of postoperative bowel injury secondary to electrocautery. These patients present with port site pain, abdominal distension, and leukopenia. If bowel injury is suspected, CT with oral contrast is the study of choice.**

If a bowel injury is recognized intraoperatively, several surgical treatment options exist depending on injury extent. If the injury is secondary to Veress needle placement only, no formal repair needs to be undertaken. Full thickness injuries to the bowel (i.e., secondary to errant trocar placement) should be resected and reanastomosed. Thermal injury to the bowels may be repaired with interrupted sutures but must be followed closely postoperatively secondary to the potential of delayed bowel perforation.

## CLINICAL PEARLS

1. Upon placing the Veress needle into the intraperitoneal space, after aspiration and irrigation, the transduced pressure should be no greater than 10 mm Hg.
2. Bowel injury secondary to electrocautery may be manifested days after surgery with isolated port-site tenderness and a low white blood cell count and should be investigated with CT of the abdomen and pelvis with PO contrast.
3. The only absolute contraindications to laparoscopic surgery are the same as for open surgery (i.e., uncorrectable coagulopathy, compromised cardiopulmonary status).
4. Port placement varies between surgeries, but in general a distance of 8 to 9 cm should exist between ports to avoid intraoperative collisions.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Discuss open and closed techniques to obtain intraabdominal access.*
2. *Discuss important anatomic landmarks during both left-sided and right-sided renal surgery.*
3. *Discuss laparoscopic anatomy of the lower urinary tract.*
4. *Discuss the effect of pneumoperitoneum on three organ systems.*
5. *Discuss common complications of laparoscopic surgery, including their prevention and treatment. Focus on vascular, bowel, and neuromuscular injuries.*

### SUGGESTED READINGS

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4. Link RE, Bhayani SB, Allaf ME, et al: Exploring the learning curve, pathological outcomes and perioperative morbidity of laparoscopic partial nephrectomy performed for renal mass, *J Urol* 173:1690–1694, 2005.
5. Menon M, Tewari A, Peabody JO, et al: Vattikuti institute prostatectomy, a technique of robotic radical prostatectomy for management of localized carcinoma of the prostate: experience of over 1100 cases, *Urol Clin North Am* 31:701–717, 2004.
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## CHAPTER 20

# Male Sexual Dysfunction

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## Introduction

Laumann and colleagues from the University of Chicago reported a comprehensive study of male sexual dysfunction in 1992. The three most common male sexual dysfunctions identified were decreased libido, erectile dysfunction (ED), and ejaculatory dysfunction (EJD). The study cohort was men ages 18 to 59. Premature ejaculation (PE), a subtype of ejaculatory dysfunction, was the most common of all the male sexual dysfunctions. Sexual dysfunction was more prevalent in women (43%) versus men (31%) and was associated with age and educational attainment.

In a follow-up study, Lindau and colleagues, also from the University of Chicago, conducted a large population survey. They reported the prevalence of sexual activity, behaviors, and problems in a national probability sample of 3005 U.S. adults (1550 women and 1455 men) 57 to 85 years of age, and described the association of these variables with age and health status. Among men, the most prevalent sexual problem was erectile difficulties (37%). Fourteen percent of all men reported using medication or supplements to improve sexual function. Men and women who rated their health as being poor were less likely to be sexually active and, among respondents who were sexually active, were more likely to report sexual problems.

**Thus there seem to be two subgroups of men with specific sexual issues based on their age. The predominant problem for the younger cohort is PE, whereas for the older cohort it is ED.**

In spite of these seemingly clear age-related divisions, clinically the waters have become a bit muddied. Data suggest that male ED that is vasculogenic in origin may start as early the fourth decade and that ED is related to garden-variety vascular risk factors such as hypertension, hyperlipidemia, and diabetes. Remarkably, ED that starts in the fourth decade may also be a strong predictor of future cardiovascular disease (CVD). From January 1, 1996, to December 31, 2005, a Mayo Clinic group (Inman 2009) biennially screened a random sample of 1402 community-dwelling men with regular sexual partners and without known coronary artery disease (CAD) for the presence of ED. The prevalence of ED was 2% for men aged 40 to 49 years, 6% for men aged 50 to 59 years, 17% for men aged 60 to 69 years, and 39% for men aged 70 years or older. The CAD incidence densities per 1000 person-years for men without ED in each age group were 0.94 (40 to 49 years), 5.09 (50 to 59 years), 10.72 (60 to 69 years), and 23.30 (70 years or older). For men with ED, the incidence densities of CAD for each age group were 48.52 (40 to 49 years), 27.15 (50 to 59 years), 23.97 (60 to 69 years), and 29.63 (70 years or older). These authors concluded that ED and CAD may be differing manifestations of a common underlying vascular pathology. When ED occurs in a younger man, it is associated with a marked increase in the risk of future cardiac events, whereas in older men, ED appears to be of little prognostic importance. Importantly, these researchers concluded that **young men with ED may be ideal candidates for cardiovascular risk-factor screening and medical intervention.**

To complicate the issue a bit further, ED and male benign prostatic hyperplasia/ lower urinary tract symptoms (BPH/LUTS) have now been linked both epidemiologically and pathophysiologically, adding importance to querying for BPH/LUTS in men with sexual dysfunction, particularly ED.

Thus ED is no longer easily subdivided by age into distinct groups. Significant age-related overlap exists because the importance of ED detection in the younger male appears to have prognostic importance for both BPH symptoms and CVD.

This backdrop now serves as the foundation for a discussion of male sexual function and dysfunction with the hope of providing some clarity and guidance to a formerly simple disease process that has now become a bit complicated.

## Peyronie Disease

Peyronie disease (PD) is an acquired penile deformity that manifests during a penile erection (curvature, indentation, hourglass deformity, or shortening). The condition usually presents with palpable induration (plaque) in the penis with or without painful erection. The symptomatic incidence of PD has been estimated at 1%. In white men the average age at onset is 53 years. The asymptomatic prevalence is estimated at 0.4% to 1.0%. PD has also been reported to occur in association with Dupuytren contractures, plantar fascial contractures, tympanosclerosis, trauma, urethral instrumentation, diabetes, gout, Paget disease, and the use of beta-blockers. This condition may occur in a familial pattern.

## BURDEN OF DISEASE

PD can cause significant psychological bother and distress and potentially strain sexual relationships. Anxiety and stress manifest in a variety of ways. In a survey of 92 men with diagnosed PD, 48% were classified as clinically depressed based on their scores on the Center for Epidemiological Studies Depression Scale. In an analysis of the prevalence of depression as a function of time since diagnosis, the percentage of PD patients with depression did not change significantly in patients with PD for less than 18 months versus those who have carried the diagnosis for more than 18 months, suggesting a lack of mental adjustment to the diagnosis of PD. Similarly, in a subset of patients who were assessed for depression at baseline and after 18 months, the percentage of patients with severe depression was not statistically different (21% versus 23%, respectively).

In addition to depression, men with PD also experience problems with psychosocial and sexual function. In interviews, patients with PD indicated that problems with functioning typically fall into one or more of four domains: (1) physical appearance and self-image, (2) sexual function and performance, (3) PD-related pain and discomfort, and (4) social stigmatization and isolation. While men with PD varied in the type and intensity of their subjective reactions to this condition, the major themes and patterns of response were consistent across groups. A questionnaire survey of men with PD also revealed a high prevalence of emotional and relationship problems.

## PATHOGENESIS

PD is a wound-healing disorder within the penis characterized by formation of a fibrous inelastic plaque, predominantly of collagen, on the tunica albuginea, the fibrous sheath surrounding the corpora cavernosa of the penis. The formation of fibrotic plaques results in penile deformities during erection including curvature, shortening, narrowing (hourglass), and bending (hinge effect). The degree to which PD limits sexual performance varies, depending on the angle and orientation of the penile curvature. Patients with mild curvature may feel slight discomfort during penetration, whereas patients with more severe curvature may be incapable of intercourse. Interestingly, some evidence suggests that the degree of curvature deformity does not directly correlate with the severity of the psychosocial bother of the disease. Men with lesser degrees of curvature may be as bothered as men with more severe deformities. The symptoms of PD are frequently accompanied by varying degrees of ED. Pain may or may not be correlated with the development of penile curvature.

The prevalence of PD is often underestimated. A survey of 152 primary care physicians (PCPs) and 98 urologists found that both urologists and, to a greater extent, PCPs underestimate the prevalence of PD and the rate of ED in patients with PD and overestimate the rate of spontaneous resolution. In addition, 44% of PCPs and 17% of urologists reported that they do not examine the penis as part of a routine physical, which the authors note is a missed opportunity to allow a patient to bring up any concerns he might have.

PD represents localized aberration of the wound-healing process. The prerequisites to the development of PD in susceptible individuals include intercourse-related penile trauma, blunt penile trauma, bleeding within the tunica albuginea of the corpus cavernosum, clustering of fibrin and the inflammatory cells, and overexpression of cytokines and growth factors, which stimulate the production of more matrix proteins and inhibit the action of metalloproteinases. Growth factors such as TGF-beta are able to recruit more inflammatory cells and thus form a vicious cycle. The outcome is a prolonged inflammatory process in a matrix of excessive but disorganized elastic and collagen fibers resulting in focal loss of elasticity of the tunica albuginea. Furthermore, PD has been commonly associated with ED. The four factors that contribute to ED are severe penile deformity preventing intercourse, a flail penis, psychological distress or performance anxiety, and impaired penile vascular function. It has also been proposed that the reduced compliance of the tunica albuginea of the plaque prevents normal compression of these veins during erection.

## CLINICAL PRESENTATION AND EVALUATION

Patients usually present in either the early or late phase of the disease process. A patient in the early phase typically presents with a nodule or plaque, painful erection, and/or penile deformity during erection. In the late phase a patient presents with a harder plaque, stable penile deformity during erection and ED. The diagnosis is easily made with detailed medical and sexual history and physical examination. A detailed psychosexual history should also be obtained that includes penile rigidity during erection, shortening, induration, hourglass constriction, or pain with or without erection, and psychological impact of the disease.

Physical examination usually detects a well-defined penile plaque or an area of palpable induration located on the dorsal surface of the penis with a corresponding dorsal penile deformity. Lateral and ventral plaques are less common but result in more coital difficulty. Penile pain may be present with erection or during sexual intercourse. Spontaneous improvement in pain usually occurs within 6 months as the inflammation settles.

Penile ultrasonography is useful in identifying the number and site of the plaques and calcification.

## TREATMENT

The treatment of PD is usually conservative at the outset. Reassurance is all that is necessary in patients with a slight curvature (less than 10 degrees) and no ED. If treatment is required, patients can be managed medically or surgically.

The efficacy of medical management of PD is difficult to determine because, in the past, few studies were properly done. Treatment is aimed at correction of the penile deformity. Medical therapies include systemic agents and local or intralesional injections. Oral systemic agents include potassium aminobenzoate, tamoxifen, acetyl-L-carnitine, colchicine, and vitamin E. In an uncontrolled study, colchicine was shown to decrease plaque size and improve penile curvature in approximately 50% of the 24 patients treated. The main side effect of the medication is gastrointestinal upset and diarrhea. Potassium aminobenzoate has been used extensively for PD, although its mechanism of action is not well understood. An extensive review of this therapy found it to be successful in 57% of cases. The most frequent side effect is gastrointestinal upset. Several reports, although small, uncontrolled, and short-term, suggest mild to moderate benefits of using tamoxifen. It is thought that tamoxifen facilitates the release of TGF-beta from fibroblasts. It has minimal side effects, including gastrointestinal distress and alopecia. Historically, vitamin E has been used to treat PD. However, a recent study compared the effects of vitamin E treatment and the natural progression of PD. They noted no significant differences between the two groups with respect to pain, bend, intercourse, and overall perception of disease progression.

Many intralesional therapies for PD have been used, including injection of calcium channel blockers, steroids, and interferons. Purified clostridial collagenase is currently under study. The use of verapamil as an intralesional agent has been studied. A prospective study showed a decrease in curvature in about 80% of the patients. The use of collagenase as an intralesional agent has been subjected to a number of double-blind placebo-controlled protocols, and, in all, good efficacy has been seen. However, collagenase is currently available only as part of clinical trials. Other mechanical devices such as the vacuum or devices for penile traction have not been adequately studied. Intralesional steroids have many local side effects, including local tissue atrophy and skin thinning with little improvement in well-established curvature.

Surgical treatment is an option for all patients including those with severe curvature or narrowing that interferes with sexual intercourse. Penile surgery should be delayed until the disease has stabilized, typically 6 to 18 months after onset. Detailed evaluation of penile vascular and erectile function (EF) is highly recommended before surgical intervention, via a penile ultrasound with an injection of a vasoactive agent to induce an erection. Patients need thorough counseling with respect to the expected outcomes and possible side effects of surgery. Historically, penile implants were the only therapeutic option for patients with severe curvature with or without preserved EF. Surgical reconstruction is generally divided into three categories: tunical shortening procedures, tunical lengthening procedures, and prosthetic procedures.

Tunical shortening procedures are performed on the convex side of the penis opposite the penile plaque. Shortening procedures are most appropriate for patients with good EF, adequate penile length, and no hourglass or narrowing type of deformity. The technique of elliptical excision of the tunica to treat PD was introduced by Pryor and Fitzpatrick in 1979. In a review of 359 men operated on between 1977 and 1992, 82% regained the ability to have intercourse. Complications reported after the Nesbit procedure include penile shortening, ED, penile hematoma, penile narrowing or indentation, urethral injury, herniation, suture granuloma, glans numbness, and phimosis. Other modifications include the Yachia procedure. Instead of removing an ellipse of tunica, a long longitudinal or multiple smaller longitudinal incisions are made in the tunica albuginea and are then closed horizontally in a Heineke-Mikulietz fashion to correct the angle of penile curvature.

Tunical lengthening procedures involve lengthening the curved, shortened side to straighten the penis; this is performed by incising or excising the plaque on the short side of the penis and placing a graft to cover the defect. Lengthening procedures are indicated in patients with severe penile curvature or narrowing or hourglass deformities. Tunical grafting met with limited success until the introduction of dermal grafts. Many autologous grafts (temporalis fascia, dura mater, tunica vaginalis, and saphenous vein), cadaveric tissue (dermis, fascia, pericardium, or porcine small intestine submucosa), and synthetic materials (polyester and polytetrafluoroethylene) have subsequently been used with varying results. Excision of the plaque has been the standard approach. However, the pathological process of PD often extends far beyond the plaque, and removing a large area of tunica albuginea may impair EF. Successful straightening was accomplished in 75% to 95% of the patients, with 5% to 13% of potent men complaining of a decrease in EF after surgery. Thus some surgeons have moved away from plaque excision and have moved to plaque incision with placement of a graft.

The use of a penile prosthesis in patients with PD is reserved for those with severe curvature with or without preserved ED that has not responded to medical management. Excellent results have been reported in the literature. Adjunct procedures during prosthesis placement include incising or excising the plaque during prosthesis placement. In most patients with mild to moderate curvature, insertion of a penile prosthesis tends to straighten the penis, and no additional procedures are necessary.

# Physiology of Sexual Function

## ERECTION

Complex interactions between physiologic, neuroendocrine, and vascular mechanisms and psychogenic interplay produce penile erection. Sexual stimulation triggers a cascade of events. In essence, **erections are neurovascular phenomena combining neurotransmission and vascular biologic responses.** A release of neurotransmitters results in smooth-muscle relaxation in both penile erectile tissue and the penile arterial walls. This transforms the penile vasculature and erectile tissues from a contracted, minimally perfused state to a relaxed, blood engorged state.

1. Functional anatomy of the penis
    a. Corporal bodies

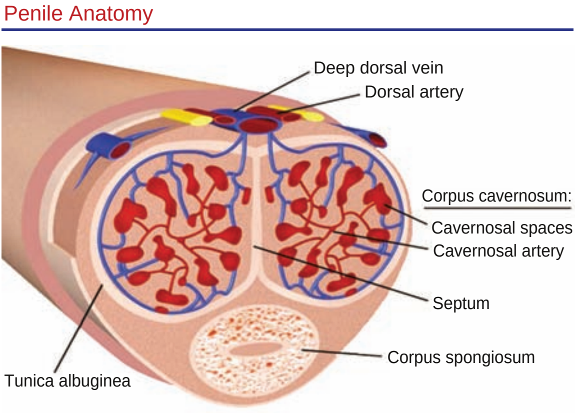

FIGURE 20-e1 The penis contains three cylindrical structures: the corpus spongiosum, which surrounds the urethra, and two erectile bodies, the corpora cavernosa. The corpora cavernosa are composed of a meshwork of interconnecting cavernosal spaces lined by vascular endothelium and are surrounded by the tunica albuginea, a tough fibroelastic covering. An incomplete septum between the corpora cavernosa lets them function as a single unit. A central artery runs through the cavernosal tissue, and postcavernous venules are located beneath the tunica albuginea. These venules merge to form large emissary veins that penetrate the tunica albuginea and then drain into the deep dorsal vein. (From Miller TA: Diagnostic evaluation of erectile dysfunction, *Am Fam Physician* 61:95–104, 109–110, 2000. As reproduced with permission, courtesy of TestosteroneUpdate.org/Causeducation.org)

The penis is composed of three cylindrical structures: the paired corpora cavernosa and the corpus spongiosum. The corpora cavernosa comprise two spongy, paired cylinders contained in the thick envelope of the tunica albuginea, which is covered by a loose subcutaneous layer underlying the skin. The tunica affords great flexibility, rigidity, and tissue strength to the penis. Between these layers of tunica run the emissary veins, which are compressed during erection, ensuring high-pressure rigidity. In the ventral groove of the tunica albuginea (between the 5 o'clock and 7 o'clock position), the outer layer is absent, leaving this area most vulnerable to penile prostheses extrusion. Each corpora cavernosum houses a network of endothelial-lined sinusoids within a trabecula of smooth muscle. An incomplete septum between them allows passage of blood from one side to the other. The terminal cavernous nerves and helicine arteries are intimately associated with the smooth muscle. In the flaccid state, the blood slowly diffuses from the central to the peripheral sinusoids. During erection, the rapid entry of arterial blood to both the central and the peripheral sinusoids expand and fill the cavernosa, producing an increase in pressure and a firm erection (Figure 20-e2).

The corpus spongiosum covers the urethra and expands distally to form the glans penis. The spongiosum is covered with only one layer of tunica albuginea, allowing low pressure during erection. The glans penis has a high concentration of nerve receptors to provide sensory input to facilitate erection and enhance pleasure.

**In corporal cavernosal tissue, nitric oxide (NO) is accepted as the principal neurotransmitter responsible for erectile response** (Figure 20-e3). With sexual arousal, NO synthase converts L-arginine and oxygen to NO. NO is also released from nonadrenergic-noncholinergic nerves and endothelial cells to cause an increase in the production of cyclic guanosine monophosphate (cGMP), a second messenger, which activates protein kinase G. NO enters into the target cell and binds to guanylate cyclase, launching a signaling pathway which ultimately produces penile cavernosal smooth-muscle relaxation via formation of cGMP. This leads to the opening of potassium channels and the closing of calcium channels, which ultimately lead to a drop in cytosolic-free calcium. This drop in calcium is the direct cause of arterial and cavernous

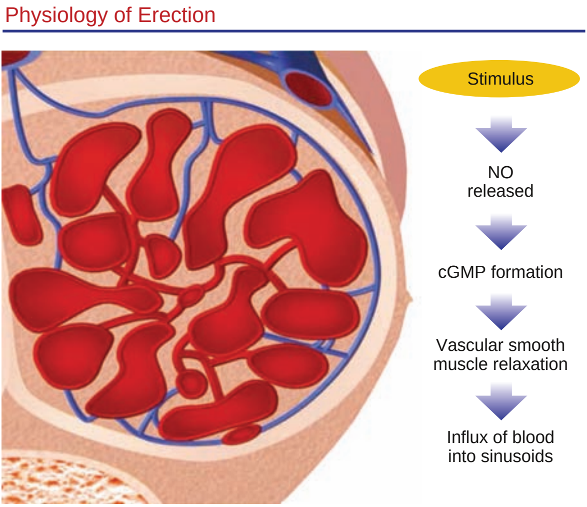
Physiology of Erection
Stimulus
NO released
cGMP formation
Vascular smooth muscle relaxation
Influx of blood into sinusoids

FIGURE 20-e2 A complex series of dynamic neural and vascular interactions is necessary for healthy erectile function (EF). When the penis is in a flaccid state, a balance between blood inflow and outflow exists in the corpora cavernosa. Venules are not compressed, and arterial vessels are constricted. Sexual stimulation triggers the release of nitric oxide (NO) into the corpora cavernosa from nonadrenergic-noncholinergic (NANC) autonomic nerves in the cavernosal tissue and sinusoids and from the vascular endothelium. NO stimulates the enzyme guanylyl cyclase to produce the intracellular mediator cyclic guanosine monophosphate (cGMP). Increases in intracellular cGMP decrease intracellular calcium and cause relaxation of vascular smooth muscle in the arteries, arterioles, and sinusoids of the corpora cavernosa. Relaxation of the penile vasculature markedly increases blood flow into the corpora cavernosa, and these erectile bodies then fill with blood, like a sponge filling with water. Entry of blood into the corpora cavernosa compresses the venules and veins under the fibroelastic covering, trapping blood in the penis. The combination of increased inflow and decreased outflow of blood leads to a rapid increase in intracavernosal pressure, resulting in penile rigidity and erection. Following ejaculation, release of catecholamines and rapid breakdown of cGMP by the phosphodiesterase type 5 (PDE-5) isoenzyme returns the penis to a flaccid state (From Miller TA: Diagnostic evaluation of erectile dysfunction, *Am Fam Physician* 61:95–104, 109–110, 2000. As reproduced with permission, courtesy of TestosteroneUpdate.org/Causeducation.org)

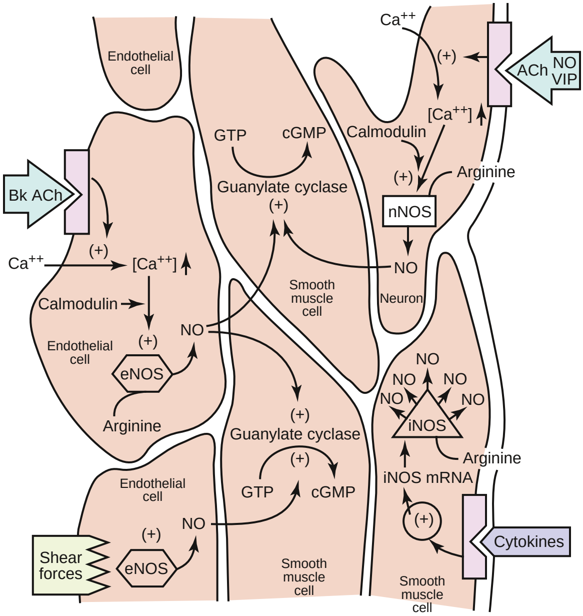

FIGURE 20-e3 Proposed mechanisms for nitric oxide synthesis (NOS), regulation, and action in the penis. Nitric oxide is constitutively formed from its precursor, L-arginine, in endothelial cells and neurons by catalytic action of endothelial NOS (eNOS) and neuronal NOS (nNOS), respectively. Whereas messenger molecules commonly activate these enzymes by signaling an influx of calcium and its binding with calmodulin, other biochemical or mechanical factors may interact with this process influencing production of NO. Once synthesized, NO diffuses to local smooth-muscle cells where it primarily activates guanylate cyclase to convert 5'-guanosine triphosphate (GTP) to 3′,5′-cyclic guanosine monophosphate (cGMP). Smooth-muscle cells represent another source of NO, but they appear to require cytokine stimulation of inducible NOS (iNOS) expression *Bk,* Bradykinin; *ACh,* acetylcholine; *VIP,* vasoactive intestinal peptide. (From Burnett AL: Nitric oxide in the penis: physiology and pathology, *J Urol* 157:320–324, 1997.)

smooth-muscle relaxation, culminating in increased penile blood flow. Thus the cyclic nucleotide signaling pathway mediates the smooth-muscle relaxing effects of NO necessary for normal EF. Down-regulation of this pathway is thought to be central to the pathophysiology of many forms of ED.

Cyclic nucleotide levels are determined by both synthesis, through the activities of guanylate cyclase on GTP, and enzymatic degradation, through the activity of phosphodiesterases (PDEs). Penile detumescence is in part the result of an increase in phosphodiesterase inhibitor type 5 (PDE-5) activity, which breaks down cGMP. The smooth muscle regains its contractile tone when cGMP is degraded by PDE-5. Competitive inhibition of the action of PDE-5 with drugs such as PDE-5 inhibitors, sildenafil, vardenafil, and tadalafil enhances erection. These drugs prevent the degradation of cGMP, allowing cGMP to act longer and produce an erection of better quality and longer duration.

## Ejaculatory Dysfunction

EJD is subdivided into premature or rapid ejaculation, delayed ejaculation, anejaculation, or retrograde ejaculation. Retrograde ejaculation occurs when the bladder neck does not close as the seminal fluid or ejaculate reaches the prostatic urethra. Thus this fluid enters the bladder instead of expulsion outside the body. Delayed ejaculation can be due to a dysfunctional nervous system, such as seen in diabetes or other neurological conditions that dampen the nervous impulses, or may be due to psychogenic causes. The same holds true of anejaculation. Psychologically, one theory is that the male is "punishing" his partner by not ejaculating. This condition can be so severe, that electroejaculation or sperm aspiration may be required to procure sperm for fertility.

Rapid ejaculation, as noted in the introduction, is enigmatic. Rapid ejaculation is the rule in the animal kingdom as the animal wishes to mate quickly to avoid predators. Humans have different motivational issues, so that the definition of *rapid* is not as clear. The historical definition is ejaculation outside the vagina or just upon entrance, within 1 to 2 minutes of an erection. The newly proposed definition is: Lifelong PE in heterosexual men is ejaculation occurring within approximately 1 minute of vaginal penetration on 75% of occasions for at least 6 months. Acquired PE is a condition in which the man suddenly ejaculates rapidly after some incident or event, whereas he was ejaculating "normally" prior to this event.

Normal ejaculatory times or latencies were described by Waldinger et al. The duration of ejaculation as measured by intravaginal ejaculation latency time (IELT) may give rise to subjective complaints of PE and is usually determined by self-assessment or by stopwatch.

Waldinger's group investigated the IELT distribution in the general male population and the accuracy of IELT assessment by using a blinded timer device instead of a stopwatch, thereby minimizing possible interference with the spontaneous and natural way of having intercourse. The IELT was measured with a timer device during 4 weeks in a nonselected sample of 474 men from the Netherlands, Spain, United Kingdom, Turkey, and the United States. Questionnaires were administered before and after the 4-week IELT assessments.

The data revealed that the IELT had a positively skewed distribution, with a geometric mean of 5.7 minutes and a median of 6 minutes (range: 0.1 to 52.1 minutes). Men from Turkey had the shortest median IELT (4.4 minutes). Men from the United Kingdom had the longest IELT (10 minutes). Circumcision and condom use had no significant impact on the median IELT. Subjects who were discontent with their latency time had slightly lower median IELT values of 5.2 minutes than the median of the population.

These help provide guidance on how to describe “normal” ejaculatory periods. PE is defined as noted above.

### TREATMENT OF EJACULATORY DYSFUNCTION

Delayed ejaculation and anejaculation caused by psychogenic issues are treated with psychotherapy.

Retrograde ejaculation can be treated with oral sympathomimetics taken within a few hours of sexual activity. PE is best treated with a combination of psychotherapy and drug therapy. There are topical agents to numb the glans penis and oral pills to delay ejaculation such as SSRIs. Other less attractive therapies include penile dorsal nerve transection and percutaneous dorsal nerve ablation.

## Pathophysiology of Erectile Dysfunction

**ED is defined as the inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function. This definition is not limited to intercourse and gives equal importance to other aspects of male sexual behavior.**

### DIFFERENTIAL DIAGNOSIS

***Erectile Dysfunction***

Psychogenic ED: Sudden onset, situational, inconsistent pattern of ED
Organic ED: Usually related to vascular risk factors, consistent pattern of ED

## ERECTILE DYSFUNCTION PREVALENCE AND MEDICAL RISK FACTORS

It is estimated that at least 10 million to 20 million American men have ED. In the National Health and Social Life Survey, the prevalence of male sexual dysfunction was 31% in a population survey of approximately 1400 men aged 18 to 59 years. Hypogonadism (5%), ED (5%), and PE (21%) were the three most common male sexual dysfunctions in this study.

The Massachusetts Male Aging Study (MMAS), a large multidisciplinary epidemiologic survey, reported the results of self-reported ED in men between the ages of 40 and 70 years and categorized their EF as completely, moderately, minimally, or not impotent. Fifty-two percent of the sample reported some degree of ED. This study demonstrated that ED is an age-dependent disorder. Between the ages of 40 and 70 years the probability of complete impotence tripled from 5.1% to 15%, moderate impotence doubled from 17% to 34%, and the probability of minimal impotence remained constant at about 17%. By the age of 70 years, only 32% of the sample reported no ED. (Figure 20-1)

In MMAS, cigarette smoking was a risk factor for total ED in men who had been treated for heart disease and hypertension and who had untreated arthritis. After the data were adjusted for age, men treated for diabetes (28%), heart disease (39%), and hypertension (15%) had significantly higher probabilities for ED than the overall sample (9.6%). Men with an untreated ulcer (18%), untreated arthritis (15%), and an untreated allergy (12%) were also significantly more likely to develop ED.

**The association between ED and hypertension, hyperlipidemia,** diabetes mellitus **(DM), and depression is documented in several studies.** This evidence supported the fact that ED shares common risk factors with these four clinical conditions. Therefore, as a pathophysiologic event, ED could be viewed as a potential observable marker for these concurrent diseases and most importantly for CVD.

## CLASSIFICATION OF ED

1. Psychogenic ED

   Male sexual behavior is complex and depends on intrinsic and extrinsic factors, including olfactory, somatosensory, and

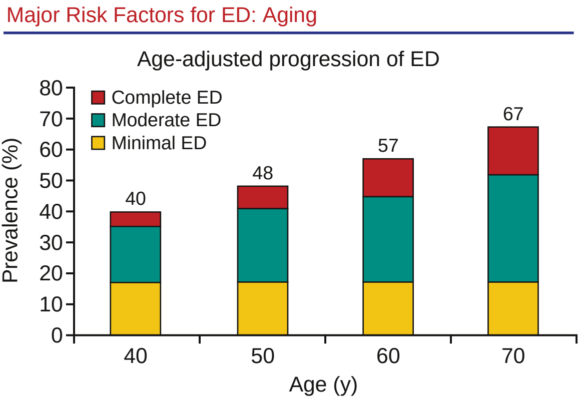

**FIGURE 20-1** The landmark Massachusetts Male Aging Study (MMAS), a community-based observational study of nearly 3000 men, aged 40 to 70 years, clearly established that erectile dysfunction (ED) is highly prevalent, age related, and progressive. Subjects (n = 1,290) were asked to respond to a sexual activity questionnaire characterizing their level of ED. *Minimal* ED was defined as "usually able to get or keep an erection;" *moderate*, as "sometimes able;" and *complete*, as "never able to get and keep an erection." Self-rated ED was reflected by higher frequency of erectile difficulty during intercourse, lower monthly rates of sexual activity and erection, and lower satisfaction with sex life and partner. In the MMAS study, 40% of men were estimated to have ED at age 40, but this increased to 67% at age 70. Age was the only variable that proved to be a statistically significant predictor of ED (P less than .0001). (From Feldman HA, Goldstein I, Hatzichristou DG, et al: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study, *J Urol* 151:54–61, 1994. As reproduced with permission, courtesy of TestosteroneUpdate.org/Causeducation.org)

visceral signals. **Most cases of ED have organic causes and less than one third is purely psychogenic.** Cortical regions of the brain, including the hypothalamus and the hippocampus, act as centers for integration of sensory stimuli and hormonal influences to initiate sexual behavior. These stimulatory or inhibitory signals act through spinal erection centers to control penile erection. Two mechanisms have been proposed for psychogenic ED: direct inhibition of the spinal erection center by the brain as an exaggeration of the normal suprasacral inhibition, and excessive sympathetic outflow or elevated peripheral catecholamine levels, which may increase penile smooth-muscle tone to prevent its necessary relaxation. Many psychological conditions, such as performance anxiety, depression, stress, low self-esteem, and personality disorders, can cause psychogenic ED.

2. Neurogenic

   Any pathology involving the brain, spinal cord, or peripheral nerves can cause ED. It has been estimated that 10% to 19% of ED is neurogenic. Onset of ED relating to the development of a neurological disability may suggest neurogenic cause for ED but does not exclude other causes of ED.

   Brain pathologies that may cause ED include temporal lobe epilepsy, hypothalamic pituitary disorders, Parkinson disease, stroke, tumors, and Alzheimer disease. Spinal cord injuries, multiple sclerosis, spina bifida, syringomyelia, multiple system atrophy, cord compression secondary to herniated disk, and Shy-Drager syndrome may affect ED.

   Peripheral autonomic nerve dysfunction is associated with ED. It can be secondary to pelvic trauma or surgical procedures or a systemic disease affecting peripheral nerves including: diabetes, uremia, amyloidosis, chronic alcoholism, scleroderma, vitamin B deficiency, systemic lupus erythematosus, or acquired immunodeficiency. Penile sensory nerves are also essential for EF. Decreased penile tactile sensitivity caused by systemic disease or aging may induce ED.

3. Endocrine causes of ED

   a. DM

      **Diabetes is a very common cause of ED in the United States. Age, duration of diabetes, HbA1c level, smoking habits, hypertension, dyslipidemia, obesity, and sedentary lifestyle are independent risk factors for ED in patients with diabetes.** ED in diabetic men is more common than retinopathy or nephropathy. ED in diabetic patients is mixed in etiology. Coexisting morbidities, psychological factors, and drugs used in diabetic patients can cause ED in diabetic patient.

      Laboratory studies looking at the causes of diabetes-induced ED have demonstrated impaired cavernosal relaxation caused by altered smooth muscle function in diabetic animals (Zhang 2012) or nitrergic dysfunction in diabetic animals. It has been shown that in animal models of type 1 and type 2 diabetes, endothelium-dependent vasodilation of cavernosal tissue is impaired because of decreased endothelial NOS (eNOS) expression or activity or increased NO scavenging.

Chronic hyperglycemia induces free-radical production which may have detrimental effect on NO-mediated cavernosal relaxation. Cavernosal hypercontractility is an underlying mechanism for ED in some animal models of diabetic ED. Cavernosal hypercontractility can result from increased sympathetic activation or intracellular contractile signaling of penile smooth-muscle cells. Venoocclusive dysfunction can also cause ED in animal models with diabetic ED.

b. Hypogonadism

In healthy young men, serum testosterone levels range from 300 to 1050 ng/dL, but it declines with advancing age. The prevalence of hypogonadism (total testosterone less than 300 ng/dL) in men aged 45 years or older is about 38%. Using a serum testosterone level of 325 ng/dL, approximately 12%, 20%, 30%, and 50% of men in their 50s, 60s, 70s, and 80s, respectively, are hypogonadal. FDA defines hypogonadism as serum total testosterone level less than 300 ng/dL, but this level is controversial. Late-onset hypogonadism is a clinical and biochemical syndrome associated with an older age group and characterized by testosterone deficiency symptoms that decrease quality of life and a total T level of approximately 350 ng/dL.

Androgens play a critical role in the physiology of EF. However, the underlying mechanism by which androgens regulate EF is not clear. In preclinical studies androgens have a physiologic role in EF. Testosterone may modulate central and peripheral mechanisms of penile erection. Androgen deficiency is associated with cavernous nerves atrophy, and androgen supplementation may regenerate the atrophied nerves. Nitrous oxide synthase (NOS) and vasoactive intestinal peptide (VIP) in the corpus cavernosum have a critical role in the relaxation of the corpus cavernosum smooth muscle and erection. It has been shown that NOS expression was reduced after reversed with androgen administration. Androgen deficiency alters smooth-muscle content and structure and increases connective tissue deposition in the corpus cavernosum.

Primary hypogonadism (hypergonadotropic hypogonadism) causes ED as a result of decreased testosterone. It can be congenital as in Klinefelter syndrome or secondary to tumor, injury, radiation, surgery, or mumps orchitis. Decreased luteinizing hormone (LH) production from the pituitary causes hypogonadotropic hypogonadism and may result from injury, tumor, or conditions such as Kallmann, Prader-Willi, or Laurence-Moon syndromes.

Hyperprolactinemia causes ED as a result of low circulating levels of testosterone because of the inhibition of gonadotropin-releasing hormone secretion by the elevated prolactin levels. Hyperprolactinemia may result from pituitary adenoma or drugs.

4. Vasculogenic

   Any vascular disease can affect the penile blood supply and cause ED. ED and cardiovascular disease share the same risk factors, including atherosclerosis, hypertension, hyperlipidemia, and cigarette smoking. It has been reported that ED in men younger than 60 years old is associated with a significant increase in the risk of future cardiac events, compared with men with no ED. It may result from the same risk factors of ED and CAD that cause underlying endothelial dysfunction.

   It has been shown that hyperlipidemia and high concentrations of low-density lipoprotein are associated with ED. In animal models, chronic hypercholesterolemia causes ED by decreasing endothelium-dependent relaxation of cavernosal smooth muscle. In rodents with cavernosal ischemia without hyperlipidemia, atherosclerotic ischemia is associated with ED secondary to decreased NOS activity and impaired endothelium-dependent and neurogenic NO-mediated relaxation of cavernosal tissue. Cigarette smoking increases oxidative stress, which causes downregulation of the NO/cGMP pathway and ED.

5. Drug-induced ED

   **Antihypertensive and psychotropic drugs are the most common medications involved in the development of ED.** Nonspecific beta-blockers and thiazide diuretics are associated with a higher rate of ED, whereas alpha-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers may tend to improve EF. The most common side effect of the more specific alpha-blockers such as tamsulosin and silodosin is retrograde ejaculation. Psychotropic drugs, including antidepressants, antipsychotics, and anxiolytics, can affect sexual function by acting on the central nervous system (CNS) and cause ED. Antipsychotics, such as risperidone and olanzapine, are associated with a higher rate of ED among psychotropic drugs. The role of statins in the development of ED is controversial.

## Evaluation of Sexual Dysfunction

### HISTORY

A thorough history should be the starting point of any evaluation of a patient presenting with the complaint of sexual dysfunction. **The diagnosis of ED can usually be made by a detailed history alone.** Often patients can assist in the diagnosis by completing a questionnaire, such as the International Index of Erectile Function (IIEF) or the Sexual Health Inventory for Men (SHIM), to assess EF before a medical interview even begins.

1. Medical history

   The clinician should first determine the general health status of any patient presenting for evaluation of ED. This initial evaluation should include a detailed medical history of diagnoses or symptoms suggesting a diagnosis of diabetes, CAD, peripheral vascular disease, chronic renal insufficiency, depression, thyroid disorders, or hypogonadism.

   A thorough medical history must also include a list of the patient's medications, specifically those which are known to be associated with ED and any medications that coincide temporarily with an onset or worsening of symptoms. Medications commonly associated with increased rates of ED include thiazide diuretics, nonselective beta-blockers, central alpha-blockers, antiandrogens, antipsychotics, antidepressants, and opiates. Finally, a medical history for the evaluation of ED should include a history of tobacco or alcohol use and a history of pelvic or perineal surgery, radiation, or trauma, including frequent or long-distance cycling. A personal and family history of CVD should be ascertained.
2. Sexual history

   The sexual history is the key portion of the evaluation of a patient presenting with the complaint of ED. The success of this evaluation with be dependent both on the data gathered during the interview and the manner in which the interview is conducted. Frequently these patients will be embarrassed or hesitant to discuss the details of their sexual dysfunction. A private setting and nonjudgmental manner can help put the patient at ease and foster a therapeutic physician-patient relationship.

The sexual history should first address the onset, duration, and extent of erectile symptoms, including an assessment of the degree of current function. Any alleviating or aggravating factors should be identified if possible. These questions should help clarify the specific complaint, differentiating ED from other sexual dysfunction such as PE, lack of interest or arousal, or anorgasmia. The onset of symptoms can help differentiate organic and psychogenic ED; organic ED usually has a gradual progression of symptoms whereas psychogenic ED often has an acute onset of symptoms. The presence of erections at night or during masturbation can also help identify cases of nonorganic ED.

3. Psychosexual history

A social history, especially inquiring about stressors at home or at work, financial or intrapersonal difficulties, activity level, and general happiness can help identify patients with depression or other nonorganic sources of low libido. Often psychogenic ED can coexist with organic ED. Identifying these patients and referring them to a psychiatric specialist can allow for concurrent treatment of their psychogenic and organic ED.

**ED can represent an opportunity for the diagnosis of CVD or modification of CVD risk factors.** Furthermore, patients with CVD may be at increased risk of acute cardiac events upon resumption of sexual activity. Therefore an evaluation of exercise tolerance and cardiac risk stratification (Figure 20-2) should be undertaken prior to the treatment of ED.

Patients should be divided into low risk, high risk, or indeterminate risk, based on their CVD status. Patients in the low-risk category include those who can perform moderately intense exercise without symptoms. This group includes patients who have treated and controlled coronary disease, hypertension, congestive heart failure (New York Heart Association [NYHA] class I or II), or mild valvular disease. These patients may undergo elective cardiac evaluation but may safely be

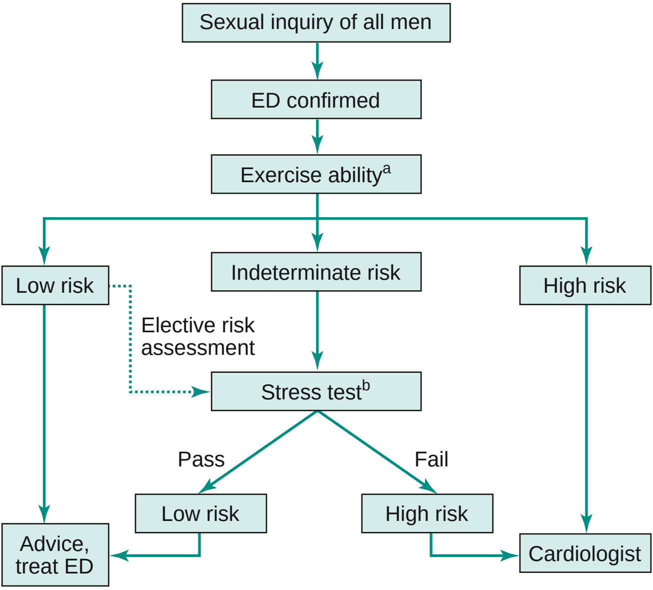

**FIGURE 20-2 Management of erectile dysfunction (ED) in all men with ED, especially those with known cardiovascular disease. [a]Sexual activity is equivalent to walking one mile on a flat surface in 20 minutes or briskly climbing two flights of stairs in 10 seconds. [b]Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.** (From Nehra A, Jackson G, Miner M, et al: The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease, *Mayo Clin Proc* 87:766–778, 2012.)

treated for ED without it. These patients can be treated with restorative medications for ED.

High-risk patients should not be treated for ED without evaluation by a cardiologist and should be counseled to avoid sexual activity until they have been treated for CVD. These patients include those with severe or uncontrolled cardiac conditions including but not limited to: angina, uncontrolled hypertension, heart failure (NYHA class IV), recent myocardial infarction, moderate to severe valvular disease, or poorly controlled arrhythmias.

Patients with intermediate risk should undergo exercise or chemical stress testing and be restratified to either low- or high-risk groups (see Figure 20-2).

## PHYSICAL EXAM

The physical exam is a relatively straightforward part of the examination of a patient with ED. This exam should include a general assessment: vital signs, height, weight, and waist circumference. It should also include basic neurologic, vascular, heart, lung, and abdominal exams. **The genitourinary portion of the exam should specifically examine the penis for abnormal curvature, plaques, lesions, and position of the urethra.** The testicular exam should evaluate the size and texture of the testicles and rule out the presence of a mass. The rectal exam should be performed to evaluate the prostate for size, nodularity, sphincter tone, and the presence of a bulbocavernosus reflex.

## LABORATORY DATA

Laboratory testing for patients presenting with ED should include a fasting lipid panel, blood glucose, and testosterone level (total or free). Additional workup is not necessary in every patient and should be ordered in patients as clinically appropriate. These optional tests include further endocrine evaluation (prolactin, estradiol, thyroid-stimulating hormone, follicle-stimulating hormone, LH, PSA) in patients with hypogonadism on initial evaluation or additional metabolic testing (creatinine, sex hormone-binding globulin, and albumin).

## SPECIAL STUDIES

Evaluation beyond the above history, physical, and basic laboratory evaluation is not necessary in all patients and should be ordered judiciously in patients for whom the results may alter treatment decisions. Usually these tests are recommended by the sexual health specialist.

1. Vascular evaluation

   Vascular evaluation can be carried out to verify vasculogenic ED because the patient with vasculogenic ED without known CVD is thought to need CVD risk evaluation. Most likely, these men are in the low-risk arm of the decision-making algorithm for ED risk stratification and will go on to therapy for their ED.

   Testing penile blood flow is particularly useful in younger patients without known CVD or in those with a history of trauma in whom abnormal penile hemodynamics are suspected. Evaluation of arterial inflow to the penis can be easily conducted using duplex ultrasonography; evaluation of venoocclusive function can be conducted by dynamic infusion cavernosometry and cavernosography (DICC). Each of these modalities utilizes intracavernosal injection of a vasodilatory agent to induce an erection that is independent of neurologic or hormonal control. Patients should routinely be monitored following vasodilator injection to ensure that iatrogenic priapism, if present, resolves with intracavernosal vasoconstrictor administration.

**Duplex Doppler ultrasonography is a noninvasive and cost-effective method of evaluating the penile vascular system and is preferred over traditional arteriography.** The ultrasound is used to first evaluate the flaccid penis, confirming normal, homogenous-appearing cavernosa without evidence of plaques or fibrosis. The size and systolic flow within the intracavernosal arteries are also assessed. Intracavernosal injection with a single or a combination of vasoactive agents such as prostaglandin E1, phentolamine, or papaverine is conducted. Once erection has been achieved or at predetermined time points, a variety of parameters, including peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI), are obtained. Decreased PSV indicates poor inflow, whereas elevated EDV or diminished RIs can indicate venous leak. The patient's self-reported degree of rigidity should be compared to his baseline level of rigidity because false-positive results can be caused by anxiety or embarrassment.

Penile arteriography is a more definitive modality for the evaluation of penile vasculature. Selective angiography of the internal pudendal artery can be undertaken to identify arterial occlusion leading to vasculogenic ED. This test should be considered in patients with abnormal duplex and a high suspicion for traumatic injury to the pudendal system (i.e., pelvic trauma, long-distance cyclists). Generally, arteriography should be reserved for patients who may undergo surgical penile revascularization.

Renewed interest in pudendal angiography and penile angiography has surfaced recently as part of a stent trial for arterial occlusive disease in men with ED (Rogers 2012). It is unclear if this area of study will continue because the results have been disappointing.

While Doppler and arteriography provide useful information about vascular inflow, evaluation of venoocclusive dysfunction is often conducted with cavernosometry and cavernosography. The penile corpora are cannulated with two needles, one to infuse saline and the other to measure pressures. After injecting a vasodilator, saline is infused into the corpora cavernosa, and intracavernous pressure is monitored. A failure of the pressure to rise sufficiently or a rapid decline in the pressure upon stopping saline infusion may be indicative of a venoocclusive dysfunction. Cavernosography, or injection of contrast into the corpora at the end of the test, can rarely identify the source of venous leak. This test has fallen out of favor with the decline in dorsal vein ligation procedures for the treatment of ED.

2. Neurologic evaluation

   The neurologic system is an important regulator of EF. As described previously, multiple pathways and centers within the CNS and PNS are involved in erection, ejaculation and orgasm. Specific tests have been developed and studied to assess the afferent somatic sensory and autonomic function at the level of the penis. Other tests record the efferent system and conduction velocities, both centrally and peripherally, in the pudendal nerve. The clinical utility of these tests remains in question and is the subject of ongoing research. Presently these tests are not recommended for routine use outside of a research setting.

3. Nocturnal penile tumescence (NPT) testing

   NPT monitoring is the study of physiologic erectile capacity in men during rapid eye movement (REM) sleep. Monitoring devices are applied which measure the number, duration, tumescence (circumference), and rigidity of erections overnight. Classically NPT testing takes place in a sleep laboratory, with observers on staff to monitor patients and correlate erections with REM sleep. Portable devices for ambulatory NPT testing also exist and allow for a less expensive and less intrusive form of NPT testing. This does, however, carry a higher rate of false positive tests because REM sleep is not confirmed in an ambulatory setting. **NPT allows for a noninvasive form of erectile testing that can differentiate psychogenic and organic ED.**

4. CV risk assessment

   In men with ED and no identified CV disease, CV risk assessment is needed. **Incident ED has a similar or greater predictive value for cardiovascular events than traditional risk factors including smoking, hyperlipidemia, and family history of myocardial infarction.** Addition of ED to the Framingham Risk Score only modestly improved its 10-year predictive capacity for myocardial infarction or coronary death data in men enrolled in the Massachusetts Male Aging Study. Other epidemiologic studies suggest that the predictive value of ED is quite strong in younger men. Indeed, in the Olmstead County Study men 40 to 49 years of age with ED had a 50-fold higher incidence of new-incident CAD than those without ED. However, ED had less predictive value (fivefold increased risk) for CAD in men 70 years and older. Identification of ED, particularly in men less than 60 years old and those with diabetes, represents an important first step toward CVD risk detection and reduction.

## Treatment

### NONSURGICAL MANAGEMENT OF ERECTILE DYSFUNCTION

As previously discussed, ED has been defined by the National Institutes of Health (NIH) Consensus Development Panel on Impotence as the "inability of the male to attain and maintain erection of the penis to permit satisfactory sexual intercourse." Inherent in this definition is the subjective nature of erectile complaints. **The expectations of *normal erectile function* may vary greatly among patients, and it is essential that the practitioner keep this in mind when treating ED. A widely accepted principle in the management of ED is the use of a goal-directed approach. Identifying *satisfactory sexual function* for an individual patient is an essential part of the treatment and can serve to limit and guide both diagnostic and therapeutic modalities.**

### LIFESTYLE

The association of ED with several systemic health conditions, such as obesity, CVD, diabetes, hypercholesterolemia, and metabolic syndrome, and with several lifestyle choices, such as smoking, alcohol abuse, and other drug use, is well known. For patients who are affected or at risk for these conditions or who smoke, drink to excess, or use drugs, lifestyle modification can be a valuable first step to treating ED. This therapeutic approach both avoids the potential side effects of other therapies and provides the benefits of improving general health and improving risk factors for other diseases.

An interesting study examined weight reduction in obese men and revealed that the purposeful treatment of obesity objectively improved sexual function versus the nonintervention group. The study was a randomized, single-blind trial of 110 obese men (body mass index of 30 or more) aged 35 to 55 years, without diabetes, hypertension, or hyperlipidemia, who had ED that was determined by a score of 21 or less on the IIEF. The study was conducted from 2000 to 2003 at a university hospital in Italy. The 55 men randomly assigned to the intervention group received detailed advice about how to achieve a loss of 10% or more of their total body weight by reducing caloric intake and increasing their level of physical activity. Men in the control group (n = 55) were given general information about healthy food choices and exercise.

After 2 years, body mass index decreased more in the intervention group, from a mean (SD) of 36.9 (2.5) to 31.2 (2.1), than in the control group, from 36.4 (2.3) to 35.7 (2.5) (P less than .001), as did serum concentrations of interleukin 6 (P = .03) and C-reactive protein (P = .02). The mean (SD) level of physical activity increased more in the intervention group, from 48 (10) to 195 (36) min/wk (P less than .001), than in the control group, from 51 (9) to 84 (28) min/wk (P less than .001). The mean (SD) IIEF score improved in the intervention group, from 13.9 (4.0) to 17 (5) (P less than .001), but remained stable in the control group, from 13.5 (4.0) to 13.6 (4.1) (P = .89). Seventeen men in the intervention group and three in the control group (P = .001) reported an IIEF score of 22 or higher. In multivariate analyses, changes in body mass index (P = .02), physical activity (P = .02), and C-reactive protein (P = .03) were independently associated with changes in IIEF score. These data suggest that diet and weight loss can improve ED.

## PSYCHOSEXUAL THERAPY

**In patients in whom a psychogenic source of ED has been identified or is suspected, referral to a therapist, especially a sexual dysfunction specialist, should be recommended.** Often psychosexual factors have some impact in ED, even for patients with an organic etiology, and those patients and their partners may also benefit from sexual counseling. Many psychotherapeutic options exist and are used by practitioners of various backgrounds. Unfortunately, convincing comparative data do not exist to suggest which of these approaches is most effective.

## TESTOSTERONE THERAPY

**Testosterone therapy is indicated only for patients with a clinical presentation suggestive of hypogonadism and low serum-testosterone levels.** The effectiveness of testosterone replacement should be monitored for clinical improvement, using measured testosterone levels, and should be stopped if clinical improvement does not occur with supplementation after a defined period of time. Testosterone supplementation carries risks of short-term male infertility, dyslipidemia, erythrocytosis, acne, gynecomastia, and increased platelet aggregation. Therefore close monitoring is required for patients on supplemental testosterone, including DRE and PSA monitoring, and PSA, blood count, lipid and liver-function testing. Testosterone replacement therapy appears to improve sexual function and quality of life over a 6- to 12-month time frame. Some suggest proceeding cautiously when considering testosterone replacement in older men.

## PHARMACOLOGIC THERAPY

1. PDE-5 inhibitors

   **PDE-5 inhibitors, by virtue of their safety, effectiveness, and ease of use, have revolutionized the treatment of ED in the United States and around the world.** Three PDE-5 inhibitors are commercially available in the United States: sildenafil, vardenafil, and tadalafil. Sildenafil was introduced in 1998, vardenafil and tadalafil in 2003. PDE-5 inhibitors have become first-line therapy for patients presenting with ED. Because of the efficacy and simplicity of PDE-5 inhibitors and the focus on goal-directed therapy for ED, many patients are treated without an additional battery of diagnostic tests. Costs of the medications remain a barrier to treatment. Proliferation of web-based, nonprescription, PDE-5-inhibitor purchasing activity has increased over the past several years for a variety of reasons. Unfortunately, counterfeit pharmaceuticals are prevalent and may place the patient at risk upon purchase.

Finally, it is important to remember the correlation between ED and CVD and the recommended cardiovascular risk evaluation in patients presenting for ED with no previous CVD history.

**Mechanistically, PDE-5 inhibitors prevent the breakdown of cGMP, thus potentiating endothelial and smooth-muscle relaxation, allowing for increased arterial inflow to the cavernosa and promoting improved erections** (Figure 20-3). It is important to note that this effect potentiates NO-mediated vasorelaxation but does not produce erection without adequate sexual arousal and the initiation of NO release in the penis.

There are 11 types of PDE with a variety of functions throughout the body. PDE-5 is found primarily in penile smooth muscle, though it also exists in the vascular and gastrointestinal smooth muscle. The majority of the side effects of PDE-5 inhibitors result from cross reactivity with PDE enzymes other than type 5 or the effect of PDE-5 inhibition

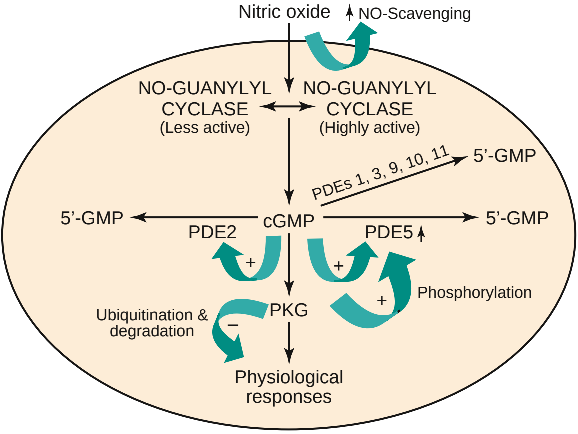

FIGURE 20-3 Negative feedback mechanisms that blunt or terminate nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) signaling. cGMP signaling is blunted and/or terminated by multiple points of action that serve to decrease cGMP level by lowering NO-GC activity, activating cGMP-hydrolyzing phosphodiesterases (PDEs), or decreasing levels of the proteins involved in the signaling. phosphodiesterases (PDEs) 1, 2, 3, 5, 9, 10, and 11 hydrolyze cGMP and are widespread throughout mammalian tissues. The activities of PDE-2 and PDE-5 can be further accelerated by allosteric cGMP binding and by phosphorylation for PDE-5. (Adapted in part from Francis SH, Corbin JD, and Bischoff E: Cyclic GMP-hydrolyzing phosphodiesterases, *Handb Exp Pharmacol* 191:367–408, 2009.)

on nonpenile PDE-5. For example, sildenafil and vardenafil slightly inhibit PDE-6, which is expressed in the retina. This cross-reactivity can explain the visual changes (light sensitivity and color vision changes) that have been observed as a side effect of these two drugs.

The three different commercially available PDE-5 inhibitors all appear to be safe and effective. All appear to have equal efficacy in treating ED, and the limited comparative data that exists does not suggest the superiority of any one of these agents. All three drugs have been shown to be effective in a variety of patient populations and for various etiologies of ED. In general, the success rate of PDE-5 inhibitors in allowing patients to achieve erections suitable for sexual intercourse is approximately 70%, though the effectiveness is reduced in diabetic patients, patients with severe ED, and in patients who have undergone radical prostatectomy.

The three commercially available PDE-5 inhibitors have pharmacokinetic differences which have important consequences for their dosing. Sildenafil and vardenafil achieve peak plasma concentrations in approximately 1 hour and have half-lives of 3 to 5 hours, whereas tadalafil peaks in 2 hours and has a plasma half-life of approximately 18 hours. The longer half-life of tadalafil allows for once-daily dosing for continuous treatment, rather than the on-demand dosing that is necessary for sildenafil and vardenafil. Sildenafil and vardenafil should not be taken with fatty meals, as they are rapidly absorbed, and delayed gastric emptying caused by fatty meals can reduce the uptake and efficacy of these medications. Tadalafil, on the other hand, has a slower absorption and is unaffected by fatty meals.

Side effects of these medications are due to their systemic effects on PDE outside of the penis. PDE-5 inhibition in vascular and gastrointestinal smooth muscle can cause headaches, facial flushing, sinusitis, dyspepsia, and hypotension. Acute hypotension is a side effect that has been reported with coadministration of alpha-adrenergic blockers and nitrates. All PDE-5 inhibitors are contraindicated in patients taking any NO donor because PDE-5 inhibitors potentiate the vasodilatory response to nitrates. Reports of nonarteritic ischemic optic neuropathy associated with PDE-5-inhibitor use have surfaced. These reports remain rare.

a. Daily PDE-5 inhibitors and use of PDE-5 inhibitors for both BPH and ED

As noted above, tadalafil, like all PDE5 inhibitors, is approved in Europe, the United States, and many other countries. The recommended starting dose for as-needed use is 10 mg, decreasing to 5 mg and increasing to 20 mg if necessary. Food does not interfere with its absorption.

Tadalafil can also be used as daily therapy for ED. The starting dose is 2.5 mg. This dose can be increased to 5 mg. A multicenter, double-blind and randomized controlled trial was conducted. In a parallel group design, 268 men were enrolled in a 1:2:2 ratio to placebo, 5 mg daily tadalafil or 10 mg daily tadalafil for a 12-week period. Primary efficacy measures included changes in the IIEF Erectile Function domain (IIEF EF), Sexual Encounter Profile diary questions 2 (SEP2: successful penetration), and 3 (SEP3: successful completion of intercourse), and tolerability. Secondary measures included the percentage of patients at the end point who reported improved EF, and the percentage who reported "no ED" (IIEF EF score 26 to 30). For patients who took placebo, tadalafil 5 mg, and tadalafil 10 mg, changes from baseline to end point were, respectively, 0.9, 9.7, and 9.4 for IIEF EF; 11.2, 36.5, and 39.4 for SEP2; and 13.2, 45.5, and 50.1 for SEP3. At the end point, 28.3%, 84.5%, and 84.6% reported improved erections, and 8.3%, 51.5%, and 50.5% reported "no ED," respectively. All comparisons between tadalafil and placebo were significant (p less than 0.001). Adverse events that occurred in at least 5% of patients were dyspepsia, headache, back pain, upper abdominal pain, and myalgia; nine patients (3.4%) discontinued because of adverse events. Again, please note that only 2.5 mg and 5 mg are approved for daily use in the United States. It is postulated that daily oral PDE-5-inhibitor use may prevent ED due to aging.

**Once-daily tadalafil 5 mg was recently approved by the FDA for daily use for the treatment of both BPH/LUTS and ED.** Data suggest that tadalafil can improve LUTS in a similar manner to alpha-blockers without the alpha-blocker side effects, though there are the PDE-5 inhibitor side effects (Egerdie 2012, Oelke 2012) .

The primary objective of the Oelke study (Oelke et al) was to compare the effect of tadalafil 5 mg once daily with placebo on LUTS/BPH. Given that the alpha-blocker tamsulosin is often a first-line treatment for LUTS/BPH, tamsulosin was included as an active control, with a secondary objective of comparing tamsulosin 0.4 mg once daily with placebo. This study was a double-blind, placebo- and active-controlled, parallel-design trial conducted at 44 urology sites in Australia, Austria, Belgium, France, Germany, Greece, Italy, Mexico, the Netherlands, and Poland. Following screening (and a 4-week washout for BPH, overactive bladder, or ED drugs, as needed), participants began a 4-week single-blind placebo lead-in period, followed by randomization (1:1:1 ratio) to once-daily tadalafil 5 mg, tamsulosin 0.4 mg, or placebo for 12 weeks. The change from baseline to week 12 (LOCF) relative to placebo in total IPSS was statistically significant for both tadalafil and tamsulosin ($p = 0.001$ and $p = 0.023$, respectively). Least squares mean (LSmean) plus or minus standard error (SE) differences in IPSS versus placebo were significant for both tadalafil and tamsulosin at 1 week (mIPSS: $-1.5 \pm 0.5$; $p = 0.003$ and $-1.5 \pm 0.5$; $p = 0.005$, respectively) and week 4 ($-2.2 \pm 0.6$; p less than 0.001 and $-2.3 \pm 0.6$; mp less than 0.001, respectively). Based on prespecified subgroup analysis, there was no significant treatment by previous alpha-blocker therapy interaction ($p = 0.230$) with respect to changes in total IPSS (Figure 20-4AB).

Importantly, tadalafil does not change the PSA at a 1-year time point (Donatucci 2011).

Sildenafil and vardenafil also improve BPH/LUTS symptoms, but neither drug has cleared the FDA regulatory hurdles for the treatment of BPH/LUTS.

2. Intraurethral agents

The intraurethral route for administration of vasoactive medications was initially developed in the mid-1990s as an alternative to intercavernosal injection. Alprostadil, a synthetic form of the naturally occurring prostaglandin E1 (PGE1), is inserted in pellet form into the urethra. It is absorbed by the mucosal lining of the urethra into the corpus spongiosum and corpora cavernosa, where it locally activates adenylate cyclase to produce cAMP and induce smooth-muscle relaxation. Unlike PDE-5 inhibitors, alprostadil does initiate erections and does not require arousal for efficacy.

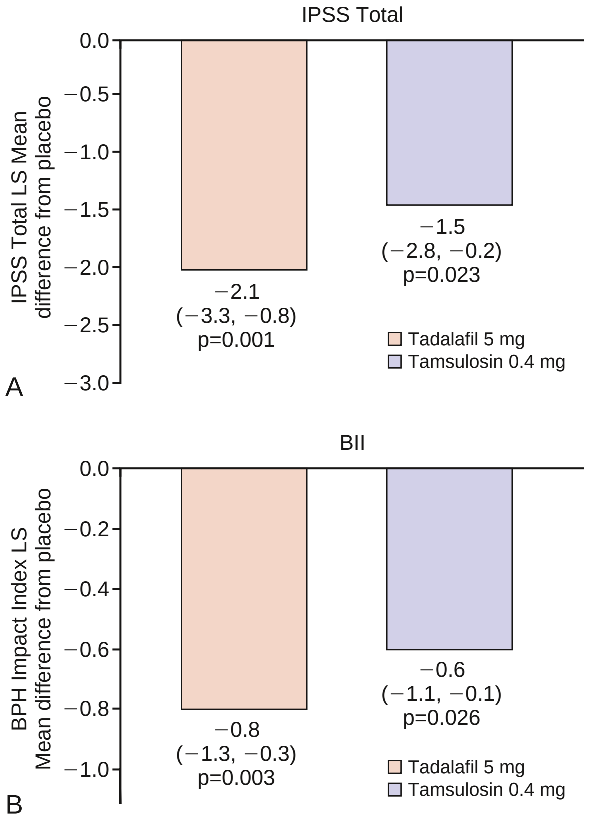

FIGURE 20-4AB Differences from placebo in (A) total International Prostate Symptom Score and (B) Benign Prostatic Hyperplasia Impact Index. Numbers represent least squares mean treatment difference (95% confidence interval) versus placebo in the change from baseline to 12 weeks (last-observation-carried-forward) and corresponding *p* values from analysis of covariance. *IPSS,* International Prostate Symptom Score; *BII,* Benign Prostatic Hyperplasia Impact Index; *LS,* least squares. (From Oelke M, Giuliano F, Mirone V, et al: Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial, *Eur Urol* 61:917–925, 2012.)

**Intraurethral alprostadil is effective in 30% to 40% of patients and can help those patients avoid more invasive intracavernous injections**. The efficacy of intraurethral alprostadil may be improved with other locally acting measures, such as vacuum constriction, or systemic therapy such as PDE-5 inhibitors. The side effects of an intraurethral suppository include local penile pain (approximately one third of patients) and, in fewer than 5% of patients, minor urethral bleeding, hypotension, dizziness, or priapism.

3. Intracavernosal injection

**Intracavernosal injection of vasoactive agents for inducing erection was first discovered in the 1980s and, as the first effective medical therapy for ED, created a paradigm shift in its treatment.** Since that time, our understanding of the physiology of erection and the introduction of intraurethral and oral systemic therapy have changed the way ED is treated. Nevertheless, injectable vasoactive agents are still commonly used in clinical practice today.

Alprostadil is the only FDA-approved injectable agent and causes erection by the cAMP-mediated mechanism described previously. It is effective in creating an erection of sufficient rigidity for sexual intercourse in approximately 60% to 80% of cases. It has the side effect of causing penile pain in approximately 11% of patients. Papaverine is a nonselective PDE inhibitor and was the first described agent for intracavernosal injection. It is less effective as a single agent than alprostadil and carries a higher rate of priapism and penile fibrosis. Consequently, it is no longer used as monotherapy for ED. Phentolamine is an alpha-adrenergic antagonist. It acts by inhibiting the postsynaptic alpha-1 receptor and effecting relaxation of the penile vasculature. Unlike the other intracavernous agents, phentolamine has significant systemic side effects, including hypotension, tachycardia, gastrointestinal upset, and nasal congestion. **Each of the intracavernosal injectable agents carries a risk of priapism, hematoma, and penile fibrosis.** Training and education regarding intracavernous injection should be provided in a monitored setting prior to self-injection, and patients naive to intracavernous injection should be observed for priapism. If priapism is detected in a timely fashion, it can usually be reversed with the injection of an alpha agonist.

Given the limited efficacy of intracavernous injection and the various side effects, administration of a combination of injectable agents has been developed. Because the mechanism of action varies for these different agents, combination therapy offers the possibility of synergistic function to improve efficacy in patients who have failed monotherapy. Additionally, lower doses can be used to avoid side effects specific to certain agents. Commonly used combinations include Bi-mix (alprostadil and phentolamine) and Tri-mix (alprostadil, papaverine, and phentolamine), which have a reported efficacy of approximately 90% in achieving erection suitable for intercourse.

4. Vacuum constriction device

   Vacuum constriction devices use external mechanical force to induce erection. An external negative pressure is created by a vacuum pump and applied to the penis, causing inflow of blood. Additionally, a constricting ring is applied to the base of the penis as a mechanical venoocclusive device, maintaining the erection. Most men report increased length, girth, and rigidity with the use of vacuum constriction, and the erection resembles a physiologic one, with engorgement of the entire penis including the glans and spongiosum. The disadvantages of this approach are penile pain and numbness, trapping of the ejaculation, discoloration and coolness of the penis, ecchymosis, and petechiae. The vacuum erection device remains a viable option for the select patient with ED.

## Surgical Management of Erectile Dysfunction

Surgery is the oldest intervention for the management of ED. Because of the variety of effective nonoperative therapies that exist for ED, surgical options are often used as a last resort in patients who have contraindications to medical therapy, cannot tolerate it, or have not benefitted from it. **Surgical therapy is also indicated in patients who have traumatic injuries or structural deformities that do not improve with medical treatment alone but may be amenable to surgical intervention.**

### PENILE PROSTHESIS SURGERY (MULCAHY 2004)

Penile implants were introduced in the 1970s and are an important option today for patients who have not had satisfactory results with nonoperative therapy. Penile implants are both efficacious and provide excellent patient and partner satisfaction.

The ideal penile prosthesis is one that provides both complete flaccidity and the closest approximation of a normal erection.

1. Indications

   Implanted penile prostheses are considered second-line therapy in most cases and usually are used after failure of less invasive treatment options, including PDE-5 inhibitors, vacuum-constriction devices, intraurethral injections, and intracavernosal injections. On occasion, a select patient may go directly to insertion of a penile prosthesis. The decision to pursue penile prosthesis surgery should include the patient and partner when possible. The patient should be counseled regarding the different available prosthesis types and their benefits and disadvantages. Manual dexterity should be evaluated to ascertain whether an inflatable prosthesis is suitable. Further, the patient should be counseled regarding his expectations of a penile prosthesis. As with intracavernosal injection, the erection produced using a penile prosthesis does not include the spongiosum or glans penis. Furthermore, the majority of penile prosthetic devices provide girth expansion only, without the increased length that accompanies natural erection. The patient's erection may be of a shorter length than his previous, natural erection. Additionally, **the sensitivity and ability to reach orgasm or ejaculate will not be affected by a penile prosthesis. A patient who is unable to reach orgasm or to ejaculate preoperatively will not regain that ability after penile implant.** It is also important to counsel the patient that infection of prosthetic material is a serious complication of the procedure, and infection will result in the need for reoperation and very likely a diminished response to future therapy for ED.
2. Types of prostheses

   Penile prostheses can be divided into two general classes: inflatable and semirigid. Semirigid prostheses are made of one unit, either malleable or mechanical. Malleable prostheses have a silicone rod over a central metal core. Mechanical implants are made up of a series of stacked disks held together by a central cable. These semirigid prostheses have the advantage of being very simple, with a low rate of failure and without requiring a lot of dexterity to operate. However, they remain at a constant girth and rigidity, making them difficult to conceal. Further, they cannot extend or enlarge, and may be too flexible during intercourse, often leaving patients unhappy with the quality of their erection.

Inflatable prostheses are composed of either two or three pieces. Three-piece inflatable implants include two corporal cylinders, a scrotal pump, and an abdominal reservoir. These implants come closest to the ideal prosthetic because they allow for girth expansion, elongation, and increased rigidity during intercourse, while also enabling easier concealment when flaccid. Additionally, as they are usually in a flaccid state, these devices put less pressure on the corpora and decrease the risk of device erosion. They are more complicated than semirigid devices and require a more complex procedure for their implantation.

Infection is the most dreaded complication of this procedure, and the use of perioperative broad-spectrum antibiotics is recommended. The duration of antibiotic prophylaxis postoperatively varies from surgeon to surgeon, but usually ranges from 2 to 7 days. The development of antibiotic impregnated devices has decreased the rate of infection, but does not eliminate the need for systemic prophylaxis. Infection occurs in less than 3% of cases, though this figure is higher for diabetics and patients with spinal cord injury. Prosthesis infection can occur at any time in the postoperative period and should always be considered in the differential diagnosis of a patient with persistent pain after implantation.

The advent of antibiotic coating of prosthesis components has significantly diminished the prosthesis infection rate.

While the gold standard of therapy is to completely remove an infected prosthetic device, this conservative approach leads to fibrosis and shrinkage of the corpora and makes reoperation significantly more challenging. An alternative salvage operation has been described which involves the explantation of a device, vigorous antimicrobial irrigation, and immediate replacement with a new device. This approach has been shown to be effective in greater than 75% of cases.

Mechanical complications are the most common, though rates have decreased since the 1970s because of improved devices. Mechanical failure may be caused by leaks in the tubing, reservoir, or cylinder, faulty connections, aneurysmal dilation of a cylinder, or pump malfunction. It is recommended that, in the setting of a mechanical complication, the entire device be explanted and replaced because subclinical bacterial colonization is prevalent and may lead to device infection. It is probably best to replace the removed prosthesis with a new, antibiotic-coated device to avoid infectious complications.

## VASCULAR PROCEDURES

Revascularization of the penis for ED is an uncommon procedure, and there is limited data as to its efficacy. Proximal disease (aortoiliac or hypogastric) is rare and can be treated via bypass grafting, endarterectomy, or balloon angioplasty. Small vessel disease (pudendal, cavernosal, or penile) can have atherosclerotic, traumatic, or idiopathic causes and can be treated by creating a direct anastomosis with the inferior epigastric artery, leading to improved inflow. In all cases, patient selection is key. Arteriography is necessary to identify the anatomic defect and conduct operative planning. Limited data indicate that **the highest success rates for penile revascularization are in young men with a traumatic etiology of arterial disease.**

Venous surgery, presumably to correct abnormal venoocclusion, has been described. Ligation or embolization of penile outflow has an anatomic basis and correlates in other fields of surgery (e.g., varicose veins). However, current data has not identified an optimal technique and this modality remains investigational.

### CLINICAL PEARLS

1. Vascular erectile dysfunction (ED) in a young man without known CVD is a prognostic indicator for future CVD.
2. Phosphodiesterase-5 (PDE-5) inhibitors remain first-line drug therapy for male ED.
3. Premature ejaculation (PE) is the most common sexual dysfunction in young men, whereas ED is the most common sexual dysfunction in older men.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What is the principal neurotransmitter responsible for erection?*
2. *Erectile dysfunction (ED) may be the first presenting symptom of what more serious condition?*
3. *Where does the parasympathetic innervation of the penis originate?*
4. *Which laboratory studies should be included in the evaluation of ED?*
5. *How does sildenafil work?*

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# CHAPTER 21

# Male Fertility and Sterility

Paul J. Turek, MD

## Background

### THE PROBLEM

1. Approximately 25% of couples will become pregnant after one month of trying to conceive. However, only **85% of couples will be pregnant after one year.** Therefore 15% of couples will have difficulty achieving pregnancy.
2. Upon evaluation, **a male factor alone may be found in approximately 30% of couples,** and both a male and female factor in an additional 20%. Thus a male factor is involved in the infertility problem in approximately 50% of cases.

## Clinical Evaluation of the Subfertile Male (Figure 21-1)

### FERTILITY HISTORY

1. Present marital history
   a. Duration of infertility
   b. Contraceptive methods and duration used
   c. Length of time trying to conceive
   d. Number of pregnancies, including miscarriages and therapeutic abortions, which indicate the potential to conceive
2. Previous marital history and relationships
   a. If the patient has attempted to conceive in the past, the duration and number of **pregnancies** should be determined.
   b. The duration and number of pregnancies conceived by the wife or partner should also be determined.
   c. Previous marriages are common. Potential fertility problems may be suspected if one partner has previously attempted to conceive without success. However, remember that the ability to conceive is a phenomenon involving both partners, and therefore is ultimately determined by the current couple.

# Reproductive Anatomy and Physiology

## EMBRYOLOGY

1. Genital organs are observed during the fifth gestational week and include an indifferent gonad, a mesonephric duct, and mullerian ducts.
2. The indifferent gonad forms from a thickening in the urogenital ridge near the mesonephros; germ cells migrate from the yolk sac to populate the urogenital ridge. These **primordial germ cells** are very closely related to **embryonic stem cells.**
3. Sexual differentiation of the embryo stems from the presence or absence of **testis determining factor** (**TDF or SRY**) located on the Y chromosome. This determines gonadal sex and forms the basis for gender-specific phenotypic development (Figure 21-e1). Early embryonic genes that can modulate the influence of SRY include **WNT-4** and **DAX1**, both of which favor **female gonadal development.**
4. Induced to form a testis, the gonad develops clustered cords of germ cells that converge to form the rete testis at the hilum of the testis. These **testis stem cells** serve as the renewing source of germ cells for spermatogenesis throughout life. To further underscore the relatedness of stem cells, human testicular stem cells can be "coaxed" into developing into cells virtually identical to **embryonic stem cells**.
5. During the eighth week of gestation, **testosterone** is made by differentiating **Leydig cells.** Hormone production declines after the twelfth week during which external genital development occurs (Figure 21-e2).

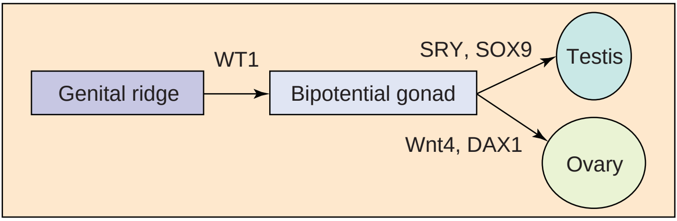

FIGURE 21-e1 Sexual differentiation of the early embryo into male gonadal sex stems from the testis determining factor (TDF or SRY) on the Y chromosome. Early embryonic genes that can modulate SRY effects include WNT-4 and DAX1, both of which favor female gonadal development.

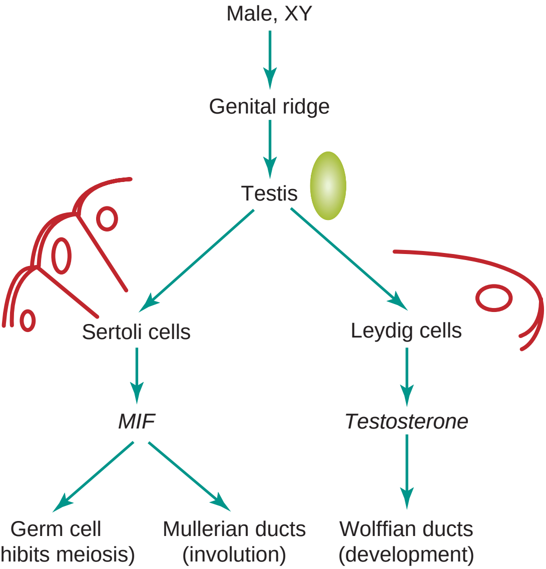

FIGURE 21-e2 Pathway of male gonadal development. Secretion of MIF (mullerian-inhibiting factor) from Sertoli cells within the early male gonad governs germ cell allocation and mullerian duct inhibition. Testosterone leads to wolffian duct development.

6. The **mesonephric duct** forms the **ureter** in both sexes and regionally specializes to form the **vas deferens** and **epididymis** in the male, joining with the testis at the **ductuli efferentes** testis.
7. The **mullerian duct** develops into fallopian tubes, the uterus, and the upper portion of the vagina in the female; in the male this development is inhibited by a **mullerian-inhibiting substance** (**mullerian-inhibiting factor; MIS, MIF**) produced by the primitive testis. Except for the **appendix testis** and **prostatic utricle,** regression is otherwise complete (see Figure 21-e2).
8. Late in gestation, the testis descends caudally along the posterior abdominal wall as a result of differential growth and through shortening of the **gubernaculum testis** within the scrotum under endocrine control. Descent into the scrotum is usually completed by birth, although it can still occur during the first year of life.

## GROSS ANATOMY (FIGURE 21-e3)

1. The male reproductive system includes the following components: the testes and seminiferous tubules, efferent ductules and rete testis, epididymides, vasa deferentia, ejaculatory ducts, seminal vesicles, prostate, penis, and urethra.
2. From the standpoint of infertility, any consideration of anatomy must also include the hypothalamic-pituitary-gonadal axis.

## REPRODUCTIVE HORMONAL AXIS (FIGURE 21-e4)

1. Components
   a. Extrahypothalamic central nervous system (CNS)
   b. Hypothalamus

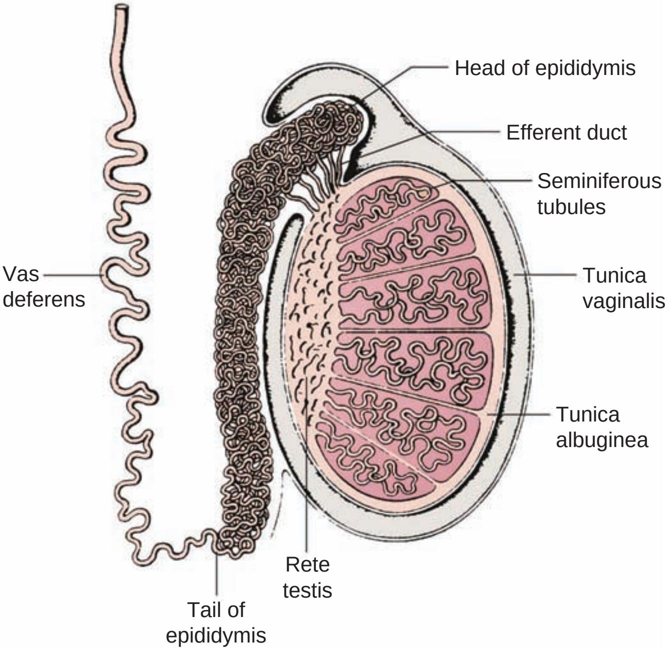

**FIGURE 21-e3 Gross anatomy of the testis, epididymis, and vas deferens.** (From Dym M. eds L Weiss and RO Greep. *Histology* ed 4, New York, 1997, McGraw-Hill, pp. 981; 1977, Elsevier Inc.)

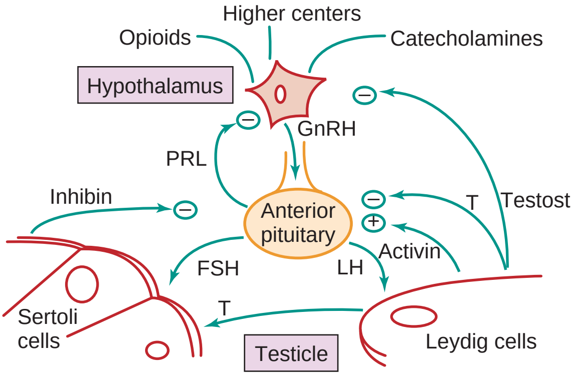

FIGURE 21-e4 The hypothalamic-pituitary-gonadal hormone axis. Both inhibitory and stimulatory feedback loops within the axis. Testosterone balance occurs in a negative feedback loop. *GnRH,* Gonadotropin releasing hormone; *PRL,* prolactin; *Testost,* testosterone; *LH,* luteinizing hormone; *FSH,* follicle stimulating hormone.

   c. Pituitary
   d. Testes
   e. Steroid sensitive organs
2. Functions
   a. Normal male sexual development
   b. Maintenance of secondary sexual characteristics
   c. Male sexual behavior
   d. Sperm production and maturation

## EXTRAHYPOTHALAMIC CENTRAL NERVOUS SYSTEM

1. The extrahypothalamic CNS exhibits a variety of stimulatory and inhibitory influences on fertility.
2. In humans, the effects of **stress** of both a physical and/or emotional nature are probably mediated through this system, but the mechanisms are unknown.

## HYPOTHALAMUS: GONADOTROPIN-RELEASING HORMONE

1. The hypothalamus is the center of integration for neuronal and humoral messages in the brain. The anterior and **ventromedial nuclei** are most important for male fertility.

2. The hypothalamus is responsible for production of gonadotropin-releasing hormone (**GnRH**) which is the primary releasing substance involved in male sexual function.

## PITUITARY: LUTEINIZING HORMONE AND FOLLICLE-STIMULATING HORMONE

1. The effect of GnRH is the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland.
2. Both LH and FSH are glycopeptides with two molecular chains. They share a common alpha chain; specificity is determined by a unique beta chain.
3. LH and FSH are secreted episodically. LH is rapidly metabolized, causing wide swings in blood concentrations when determined by radioimmunoassay techniques. Occasionally, more accurate LH levels are needed; this is done with pooled blood samples. FSH is more slowly metabolized, resulting in a more constant level within the bloodstream.
4. The testes are the primary target for LH and FSH. No other target organs for these hormones have been found.

## THE TESTES

1. Microscopic anatomy
   a. **Seminiferous tubules comprise the bulk** (**80%**) of the **testis mass** and are responsible for sperm production. Thus testis atrophy generally suggests a low sperm count.
   b. The **interstitium** between the seminiferous tubules contains blood vessels, lymphatics, and **Leydig cells**.
2. Seminiferous tubule structural organization
   a. The tubules consist of long ducts lined by **Sertoli cells** that engulf and nurture developing germ cells.
   b. Sertoli cells have membrane receptors that bind FSH, resulting in increased intracellular cAMP and subsequent cytoskeletal reorganization for protein synthesis.
   c. The primary secretion products from Sertoli cells include MIS in the fetus, androgen-binding protein (ABP), transferrin, and inhibin (a nonsteroidal glycoprotein) in the adult.
   d. Sertoli cells regulate the tubule microenvironment. They govern fluid secretions into the lumen of the seminiferous

tubules and partake in phagocytosis, steroid metabolism (in part), sperm production, and sperm movement through the tubule.

   e. Sertoli cells are also mainly responsible for the **blood-testis barrier.** This anatomic barrier is surrounded by **myoid cells** and consists of the basement membrane and Sertoli cell **tight junctions.** In addition, a selective physiologic barrier is created by active transport processes across Sertoli cells. Further compartmentalization is established as Sertoli cells divide, developing germ cells into two areas, the **basal compartment** for immature germ cells and stem cells and the **adluminal compartment** for germ cells undergoing differentiation and maturation. This complex blood-testis barrier provides an **immunologically privileged site for mature spermatozoa** because these haploid cells harbor unique and specific antigens that are not otherwise recognized as "self" by the body's immune system.

3. Seminiferous tubules: spermatogenesis
   a. **LH, FSH, and testosterone are all required for normal spermatogenesis.**
   b. Sertoli cells, lining **250 meters** of seminiferous tubules in the average testis, regulate the complex process of spermatogenesis.
   c. A variety of germ cell types exist, including **spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids, and spermatazoa.** Fourteen germinal cell subtypes are recognized histologically and are associated with six distinct stages of spermatogenesis. Certain early-stage spermatogonia are actually adult testis stem cells and are the source of the constantly self-renewing germ-cell lineage. Spermatids and spermatozoa have a **haploid** complement of chromosomes.
   d. The process of spermatogenesis takes about **60 days** to complete. The average **daily output is 125 million spermatozoa,** which declines with age. A normal man makes 1200 sperm for every heartbeat.
   e. **Spermiogenesis is the maturation process of a spermatid to a spermatozoan.** This includes nuclear condensation and a programmed repackaging of DNA from histones to protamines, acrosome formation, residual body separation from the sperm, and tail formation. It is one of the most complex series of morphological changes undertaken by any mammalian cell.

4. Interstitium: Leydig cells
    a. Leydig cells contain membrane receptors that bind LH, resulting again in cAMP production, protein kinase activation, and protein phosphorylation.
    b. LH stimulation results in the conversion of cholesterol to testosterone in a steroidogenic pathway.
    c. Testosterone diffuses into the plasma (**endocrine** function) or into the seminiferous tubule lumen (**paracrine** function). In the plasma, **testosterone is bound** (98%) **to sex hormone-binding globulin** (SHBG) **or albumin**. Within the seminiferous tubules, testosterone is bound to ABP.
    d. Depending on the target tissue, testosterone may be active itself or may be reduced to **dihydrotestosterone** (**DHT**) by the enzyme 5-alpha reductase.
    e. Testosterone is responsible in part for sexual differentiation, spermatogenesis, gonadotropin regulation, sexual maturation, and behavior.

## FEEDBACK MECHANISMS (SEE FIGURE 21-e4)

1. GnRH, LH, and FSH are generally thought to be responsible for driving the production of testosterone and spermatozoa as noted above. Feedback mechanisms regulate the production and release of these substances.
2. LH regulation
    a. Testosterone and estradiol are the major **negative-feedback** substances that control the formation and release of LH.
    b. **Testosterone therefore regulates its own production** by acting on the pituitary and hypothalamus. This has implications for clinical care: **Exogenous testosterone supplements will suppress both endogenous testosterone (through decreased LH) and sperm production (through decreased FSH).**
    c. **Estradiol is produced within the testicle and the liver upon conversion from testosterone (5-alpha reductase).** It is found in smaller amounts within the blood stream (testosterone:estrogen ratio is typically 10:1) but is potent in action. The site of regulation is also at the level of the pituitary and hypothalamus.
3. FSH regulation
    a. Testosterone and estradiol are the major modulators of pituitary FSH secretion. This is why exogenous testosterone supplements suppress spermatogenesis.

   b. In man, Sertoli cells produce **inhibin**, a two-subunit hormone in the transforming growth-factor family, which has an inhibitory effect on pituitary FSH output. In contrast, **activin**, a glycoprotein formed as a homodimer of either inhibin chain, has a stimulatory effect on pituitary FSH. Neither inhibin nor activin affects pituitary LH release.
4. A variety of short feedback loops and other modulating substances more finely tune this system.

## TESTICULAR TRANSPORT

1. As noted above, movement of developing germ cells from the basement membrane to the lumen and release into the lumen of the seminiferous tubules is controlled by Sertoli cells. Unlike most mammalian species, **the stages of spermatogenesis occur in a patchwork pattern** within the seminiferous tubules. This, in combination with constantly renewing cycles of spermatogenesis, **ensures that sperm production is continuous in nature.**
2. The movement of the spermatozoa from the testis to the epididymis is controlled by four factors:
   a. Fluid pressure generated within the seminiferous tubule
   b. Myoepithelial contractions of the seminiferous tubules
   c. Contraction of the tunica albuginea of the testis
   d. Cilia within and contraction of the wall of the efferent ductules
3. The spermatozoa enter the epididymis in an immature state.

## EPIDIDYMAL FUNCTIONS

1. Transport and storage
   a. The spermatozoa traverse the length of the epididymis in **12 days**. This process is governed by regular slow contractions of the muscular wall in a fashion similar to intestinal peristalsis.
   b. Approximately **700 million sperm are stored within the epididymides and vasa deferentia**. Approximately 60% of these are stored within the tail (cauda) of the epididymides. Sperm become progressively more motile as they traverse the epididymal tubules, knowledge of which is important in harvesting sperm from the epididymis for in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

   c. At the time of **emission**, regular coordinated contractions of the tails of the epididymides and the vasa deferentia occur, mediated by the sympathetic nervous system, propelling sperm into the prostatic urethra. During **ejaculation**, somatic nervous system-stimulated rhythmic contractions of periurethral and pelvic floor muscles propel the sperm through the urethra in the presence of a closed bladder-neck closure mediated by the sympathetic nervous system.

2. Sperm maturation
   a. The chemical composition of the intraluminal fluid changes significantly in the three anatomic portions of the epididymis.
   b. A variety of sperm membrane changes in permeability and antigenicity also occurs.
   c. **Motility and fertilizing capacity** are gained during transport through the epididymis.
   d. The final process of maturation, **sperm capacitation**, takes place after the sperm have been ejaculated and come in contact with the female reproductive tract. **Fertilizing capacity** lasts approximately **48 hours** within the external female genitalia, an important finding for counseling patients on the optimum frequency of sexual intercourse around the time of ovulation.

## SEMEN COMPOSITION

1. The bulk of seminal fluid originates from the accessory ducts, with the spermatozoa adding a small (less than 10%) amount to total volume.
2. Prostatic fluid
   a. The **prostatic fluid** is usually found in the first part of the ejaculate and contributes approximately **one quarter of the total volume. This fluid is acidic (pH less than 6.5).**
   b. Specific prostate products include liquefaction factors such as **prostate-specific antigen (PSA)**, zinc, citric acid, acid, phosphatase, and spermine. The latter substance, when oxidized to aldehydes, produces the characteristic odor of semen.
   c. **PSA, a 33-kd molecular weight serum protease in the family of glandular kallikreins, serves to liquefy the coagulum** of human semen 5 to 20 minutes following ejaculation.

3. Seminal vesicle fluid
   a. The **seminal vesicle fluid** is usually found in the second part of the ejaculate and contributes approximately **two thirds of the total volume. This fluid is basic** (**pH greater than** 7.0**).**
   b. Specific substances secreted by the seminal vesicles include coagulation factors, prostaglandins, and fructose. **Fructose** is measured on a semen analysis to investigate the diagnosis of ejaculatory duct obstruction.

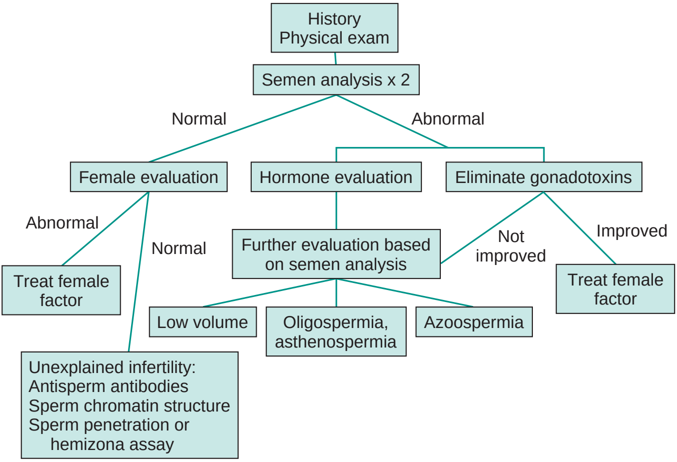

FIGURE 21-1 Algorithm for diagnostic evaluation of male-factor infertility. (From Turek PJ: Practical approaches to the diagnosis and management of male infertility, *Nat Clin Pract Urol* 2:226–238, 2005.)

3. Sexual history
   a. Frequency of intercourse and masturbation: Overly frequent (daily) or infrequent (more than 48 hours apart around the time of ovulation) can adversely affect the couple's ability to conceive.
   b. Libido, potency, and sexual technique: A normal desire and ability to have intercourse is critical, and problems in these areas are often overlooked by clinicians. **Situational erectile dysfunction** (ED) caused by stress is common among couples trying to conceive and is easily treated with **phosphodiesterase inhibitors**.
   c. Ejaculation: This needs to occur deep within the vagina. Severe problems with **premature ejaculation, chordee, or severe hypospadias** may prevent proper deposition of sperm.
   d. **Dyspareunia** and the use of lubrication: Impaired natural vaginal lubrication can result in painful intercourse for either partner. Most lubricants are spermicidal. The use of **vegetable oil-based** substances is safe for sperm.
   e. Understanding of the **ovulatory cycle:** It is important that the couple understand when ovulation occurs and have timed intercourse regularly during this time. There is evidence

that "front loading" sexual intercourse, having more before rather than after ovulation, might improve pregnancy rates.

4. Genitourinary history
   a. Testicular descent: Bilateral **cryptorchidism** is associated with impaired spermatogenesis and fertility. With unilateral maldescent, fertility potential slightly decreases.
   b. Sexual development and onset of puberty: **Delayed puberty** can indicate syndromes (e.g., Kallmann) or chromosomal issues (e.g., XXY).
   c. Infections: Venereal, nonvenereal, mumps (at the time of puberty or later), recent febrile illness, or other infectious problems that directly involve the genitalia or urogenital duct system may be associated with a significant scarring and subsequent fertility problems. Viral infections and other febrile illnesses not specifically involving the genitalia may also temporarily lower sperm counts.
   d. **Trauma or torsion:** Either condition may injure the duct system or result in ischemic damage to the seminiferous tubules.
   e. Exposure to chemicals: A variety of drugs and industrial compounds may be associated with abnormal semen analyses. **Industrial solvents** are the most concerning.
   f. Exposure to heat: Prolonged exposure to high temperatures may adversely affect spermatogenesis. **Hot tubs, hot baths, saunas, or steam rooms on a regular basis can be significant in this regard**.
   g. Exposure to radiation: Even small amounts of ionizing radiation, particularly that used for medical therapy, may destroy sperm-forming cells. **Spermatogonia are particularly radiosensitive.**
5. Previous infertility evaluation
   a. Patient: A history of previous semen analyses and medical or surgical treatment is certainly important for the etiology and prognosis of male infertility.
   b. Wife or partner: It is wise to understand the fertility potential of the partner (see Figure 21-1). Obviously, conception involves two people and if for some physiologic or anatomic reason, an irreversible problem exists in the female partner, pregnancy is unlikely. The evaluation of each partner should be carried out simultaneously, and the male evaluation should be completed prior to invasive procedures on the female partner. **At least 1 year of maternal**

**reproductive potential should exist for the best outcomes after male infertility treatment.**

## GENERAL MEDICAL HISTORY

1. While most conditions causing male infertility do not lead to long-term medical consequences, **1% to 2% of men undergoing evaluation for infertility will have a significant underlying medical condition.**
    a. Medical illnesses: Medical problems such as **diabetes** and **hypertension** or their pharmacologic treatments may adversely affect erectile and ejaculatory function and hence fertility.
    b. Abnormal metabolism of sex steroids may be associated with various liver and renal diseases and interfere with the regulatory mechanisms of spermatogenesis. Rare medical illnesses such as **Young syndrome** (immotile cilia syndrome) and **Kartagener syndrome** (ciliary defect with situs inversus) can adversely affect fertility.
2. Surgical history
    a. Inguinal herniorrhaphy, particularly when performed on a young child and when performed bilaterally, may be associated with injury to the vas deferens in 1% to 2% of patients.
    b. Surgery on the ureter, bladder, bladder neck, or urethra may result in problems with emission and/or ejaculation.
    c. Retroperitoneal surgery and other major pelvic procedures may result in failure of emission and/or problems with retrograde ejaculation. Young males with nonseminomatous testis tumors are treated with retroperitoneal lymphadenectomy and subsequently have fertility problems caused by absent ejaculation from either failure of emission or from retrograde ejaculation. It appears that two to three cycles of adjuvant chemotherapy often given in lieu of retroperitoneal lymphadenectomy do not significantly impair male fertility.
3. Current and past medications
    a. A variety of drugs and chemotherapeutic agents may adversely affect sperm production and/or function. Adverse affects are usually reversible upon discontinuation (Box 21-1).
4. Occupation and habits
    a. Occupation and stress: The effects of daily stress on fertility are poorly quantified. **Severe, acute stress has been associated with decreases in ejaculate volume and sperm count.** While most patients inquire about stress, it is unlikely that

### BOX 21-1 **Drugs and Chemicals with Potential Adverse Fertility Effects**

Alcohol
Alkylating agents (e.g., cyclophosphamide)
Arsenic
Aspirin (large doses)
Caffeine
Cimetidine
Colchicine
Dibromochloropropane (pesticide)
Diethylstilbestrol (DES)
Finasteride
Lead
Monoamine oxidase inhibitors
Marijuana
Medroxyprogesterone
Nicotine
Nitrofurantoin
Phenytoin
Spironolactone
Sulfasalazine
Testosterone

they would change their job or lifestyle, making this problem difficult to treat. Encouraging regular exercise, yoga, or acupuncture may help reduce stress.

   b. The active ingredients in **cigarettes, marijuana, coffee, tea, alcohol,** and some naturopathic herbs have been demonstrated in laboratory studies to be potentially gonadotoxic. The susceptibility of individuals to these substances varies widely and is difficult to quantify.

5. Family history
   a. Sibling fertility status may identify familial conditions such as cystic fibrosis, genetic infertility due to Y chromosome deletions, and congenital adrenal hyperplasia.
   b. In utero exposure to **diethylstilbestrol (DES)** may result in testicular, epididymal, and penile anatomic abnormalities. Despite the finding of impaired semen quality in DES-exposed men, proof of decreased fertility is not obvious in extensive follow-up studies.

## PHYSICAL EXAMINATION

1. General examination: This evaluates the patient's **body habitus** and secondary sexual characteristics. In particular, the pattern of hair distribution and **gynecomastia** can reflect endocrine disorders.
2. Examination of the genitalia: The genitalia are the most important aspect of the examination. This should be performed in a systematic fashion, taking care to evaluate the following areas:
    a. Penis: The size of the penis and location of the meatus are important in assuring the delivery of spermatozoa deep within the vagina at ejaculation.
    b. Testes: The **location, size, and consistency** of the testes should be noted. The testes should lie dependently in the scrotum. Testicular size is particularly important, as the bulk of the testicle (80%) relates to sperm production. The size of each testis can be compared to the other testis and to normal values by noting the length and width of the testicle or by attempting to quantify the volume by comparison to plastic models of known volumes. The normal testicle in the adult is greater than **4 cm in length** and greater than **2.5 cm in width (volume: 20 mL).** Each testicle should have a firm consistency. Ethnic variations in testis size are well described.
    c. Epididymides: The epididymides should be examined for size and consistency. The **obstructed epididymis feels enlarged and firm.** The epididymis that is scarred from either trauma or chronic infection may be hard and irregular. Part of the epididymis may be missing in association with congenital absence of the vas deferens.
    d. Vasa deferentia: Each vas deferens should be palpable as a distinct, firm, cordlike structure in the scrotum. In **1% to 2% of infertile men, one or both vasa are not palpable in the scrotum, a condition termed *congenital absence of the vas deferens (CAVD)*.**
    e. Spermatic cords: Each spermatic cord should be evaluated for size and consistency with the patient in the upright and supine positions. The patient should be asked to perform a Valsalva maneuver while standing to accentuate differences in blood volume within the cord, characteristic of a **varicocele**. The internal spermatic veins fill while standing,

   and this filling may be increased when the Valsalva maneuver is performed. In the supine position, these veins drain more easily, and hence the varicocele is not as easily palpable. Persistent fullness in the spermatic cord upon reclining is suggestive of **cord lipoma** and not varicocele. Other abnormalities of the spermatic cord include **hydrocele and spermatocele**, both of which may be detected during this examination.
   f. Inguinal region: The inguinal canals are palpated for hernias. In addition, the inguinal regions should be inspected to assess if previous surgery may have injured the vasa deferentia or testicular blood supply.
3. Rectal examination: This should be performed to detect lower gastrointestinal pathology and to palpate the prostate and seminal vesicles. The prostate should be small and benign in consistency without tenderness or bogginess. The seminal vesicles are generally not palpable under normal conditions but may be palpable with obstruction of the ejaculatory ducts.

## SEMEN ANALYSES

1. Collection: Generally at least **two semen analyses** are needed to establish a baseline for a patient. If a discrepancy exists, a third or perhaps even a fourth specimen may be required. Each semen analysis is collected after **3 days of abstinence**. The specimen is generally collected by masturbation into a clean, dry container and examined within 1 hour. If the specimen is collected at home, it should be kept near body temperature during transport to the laboratory (shirt pocket). The patient should avoid lubricants during specimen collection. If needed, silicone condom devices are available.
2. Minimal standards of adequacy: While there is no absolute measure of fertility on semen analysis, minimal standards of semen adequacy have been defined by the World Health Organization (Table 21-1).
3. Additional physical parameters: Other properties are examined at the time of a routine semen analysis. These include:
   a. Color: The semen is generally grayish-white in color with an opalescent character. It may also appear lumpy.
   b. Coagulation: This occurs immediately after ejaculation.

TABLE 21-1 **Semen Analysis: WHO 2010 Minimal Standards of Adequacy**

| | |
|---|---|
| ***Seen on at least two occasions:*** | |
| Ejaculate volume | 1.5-5.0 mL |
| Sperm density | >14 million/mL |
| Motility | >40% motile |
| Forward progression | >2.0 (scale 0-4) |
| Morphology (strict) | >4% normal |
| ***And:*** | |
| No significant sperm agglutination | |
| No significant pyospermia | |
| No hyperviscosity | |

*WHO,* World Health Organization.

c. Liquefaction: This occurs 5 to 30 minutes following ejaculation. **PSA** is the serine protease responsible for this process.
d. Viscosity: This parameter refers to the fluid consistency of the semen after coagulation and liquefaction have occurred. Viscosity is normal if it is possible to pour the semen in a drop-by-drop fashion.
e. pH: The pH of semen is normally in the range of 7.2 to 8.0. A low pH implies absence or blockage of the seminal vesicles because the ejaculate consists entirely of acidic prostatic fluid.
f. Fructose: As noted above, fructose is produced by the seminal vesicles. Semen fructose is examined in cases of azoospermia with low ejaculate volume (less than 1.5 mL). Absence of fructose in semen suggests absence of the vasa deferentia and seminal vesicles, ejaculatory duct obstruction, or dysfunction of the seminal vesicles.

## OTHER LABORATORY TESTS

1. Urinalysis: This test is useful to rule out infection of the lower genitourinary tract and associated glandular structures.
2. Endocrine evaluation: A complete hormonal evaluation includes measurement of serum LH, FSH, testosterone, and prolactin. However, **99% of endocrine conditions can be detected through the initial measurement of serum FSH and testosterone.** Hormonal testing can differentiate between hypogonadism caused by hypothalamic or pituitary disease and that caused by primary testicular failure.

3. Other tests routinely recommended in the past are now unnecessary. These include tests of **thyroid** and **adrenal function** (less than 0.5% of cases). **Prolactin** levels should be obtained if low testosterone is found or if the patient has gynecomastia, severe headaches, or visual disturbances. Prolactin-secreting pituitary tumors produce high levels of circulating prolactin, and these lesions tend to reduce LH and FSH levels.
4. Genetic testing: **Karyotype analysis is critical for all men with azoospermia and severe oligospermia** (**less than 5 million sperm/mL**) **who are planning IVF and ICSI.** In addition, it is now known that specific deletions in the Y-chromosome are found in approximately 15% of men with azoospermia and 5% to 8% of men with severe oligospermia. Several regions of the long arm of the Y chromosome have been classified as **azoospermic factor (AZF) regions** (Figure 21-2). **Most deletions are found in the AZFc region in a specific gene complex termed *DAZ (deleted in azoospermia)*. Deletions in these regions appear specific for infertility.** Deletions of AZFa and AZFb have a much poorer prognosis for testicular sperm retrieval than patients with AZFc deletions.
5. Tests of sperm function
    a. **Sperm morphology:** Sperm cytology is an indirect measure of sperm quality. By assessing the dimensions and shape characteristics of the sperm head, midpiece, and tail, sperm can be classified as *normal* or not. In the strictest classification system (Kruger morphology), only 4% of sperm in the ejaculate are typically deemed normal. This number has been correlated with the success of egg fertilization in vitro. In addition, **sperm morphology is an indicator of testicular health** because shape characteristics are determined during spermatogenesis. Sperm morphology complements other information to better estimate the chances of fertility.
    b. **Sperm chromatin assay:** The structure of sperm chromatin (the DNA-associated proteins) is independent of semen quality and can be measured by COMET and TUNNEL assays and by flow cytometry after acid treatment and staining of sperm with acridine orange. These tests assess the degree of DNA fragmentation and indirectly reflect the quality of sperm DNA integrity.

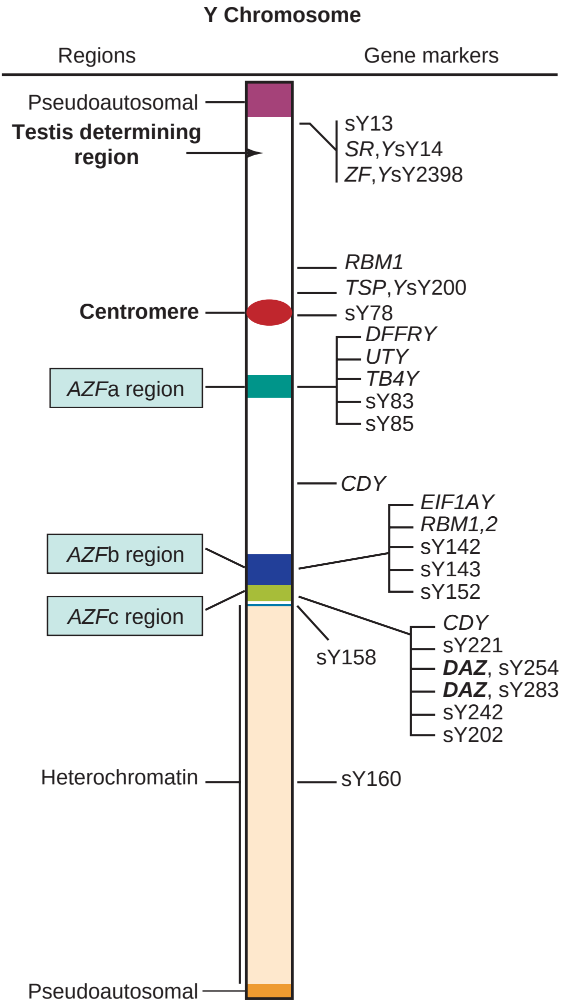

FIGURE 21-2 Schematic diagram of the human Y chromosome with known regions and genes listed. The testis determining region (SRY) is shown on the short arm (Yp) of the chromosome. AZF a,b,c denote the azoospermia regions of the chromosome that are associated with infertility.

**Abnormally fragmented sperm DNA rarely occurs in fertile men, but can be found in 5% of infertile men with normal semen analyses and 25% of infertile men with abnormal semen analyses.** This test can detect infertility that is missed on a conventional semen analysis. Often reversible, causes of DNA fragmentation include tobacco use, medical illness, hyperthermia, air pollution, infections, and varicocele.

6. Antisperm antibodies: A link between infertility and antisperm antibodies has been recognized for years. **The effect of antibodies is to disturb either sperm transport through the female reproductive tract or sperm-egg interaction.** Enzyme-linked immunosorbent assay (ELISA) and immunobead binding assay are two commonly used tests to detect antibodies on sperm.
7. **White blood cells:** Reproductive tract infections are a treatable cause of infertility and are often heralded by the presence of excessive white blood cells in the ejaculate (**pyospermia or leukocytospermia**). Special stains can distinguish white cells from immature germ cells, the latter of which are not pathologic.

## RADIOLOGIC PROCEDURES

1. **Transrectal ultrasound (TRUS):** This is indicated in infertile men with low-volume ejaculates (less than 1.5 mL) **Ejaculatory duct obstruction (EDO)** may be identified by seminal vesicle dilatation (greater than 1.5 cm in diameter). However, seminal vesicle hypoplasia or absence is also easily diagnosed. Often EDO caused by stones, scar, cysts, or a persistent utricle can be diagnosed by TRUS.

   Although informative, TRUS is considered a *static* imaging technique that is not entirely specific for EDO. Therefore *dynamic* imaging studies are now recommended along with TRUS to increase the accuracy of the EDO diagnosis. **Seminal vesiculography, chromotubation** (antegrade injection of diluted indigo carmine monitored by flexible cystoscopy), or **ejaculatory duct manometry** are three dynamic tests that improve the accuracy of the EDO diagnosis. **Seminal vesicle aspiration** is also used to confirm the presence of sperm in patients with suspected obstruction.

2. **Vasography:** Intraoperative, transscrotal vasography is currently used to detect abdominal vas deferens, seminal vesicle, and ejaculatory duct patency prior to definitive surgery for epididymal or vasal obstruction. It is typically performed simultaneously with microsurgical reconstruction.
3. **Scrotal ultrasound:** This is indicated when the testes are not easily palpable because of coexistent hydrocele, to confirm the origin and character (solid versus cystic) of intrascrotal masses, and for confirming a clinically suspicious varicocele. Level I evidence suggests that finding and treating subclinical varicoceles will not improve male fertility.

## Classification of Abnormalities

### GENERAL INFORMATION

1. A variety of classification schemes exists to categorize fertility problems. One of the most useful is based on the findings on semen analyses with initial classification of problems into one of four categories: (1) all parameters normal, (2) azoospermia, (3) a single abnormal parameter, and (4) multiple abnormal parameters. The decision to treat a semen abnormality to improve fertility depends in part on maternal reproductive potential and also on how correctable the problem is, as outlined in Figure 21-3.

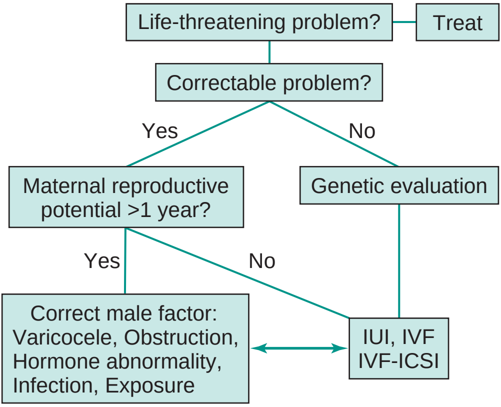
Life-threatening problem?
Treat
Correctable problem?
Yes
No
Maternal reproductive potential >1 year?
Genetic evaluation
Yes
No
Correct male factor: Varicocele, Obstruction, Hormone abnormality, Infection, Exposure
IUI, IVF
IVF-ICSI

FIGURE 21-3 Algorithm for treatment of male infertility. (From Turek PJ. *Nat Clin Pract Urol*. 2:1-13, 2005.)

2. Distribution of semen abnormalities among infertile men: azoospermia 8%, single abnormal parameter 37%, and multiple abnormal parameters 55%. Among isolated abnormal parameters, impaired sperm motility accounts for the majority of cases.

## ALL PARAMETERS NORMAL

1. When two semen analyses are normal and the history and physical examination are unrevealing in the male, further evaluation of the female partner is recommended.
2. If the evaluation of the female partner is also found to be normal, and the couple still has not conceived, then sperm-function tests noted above (i.e., sperm chromatin assay, sperm morphology) may be useful. Most couples with unexplained infertility will go on to be treated with **intrauterine insemination (IUI) or IVF.**

## AZOOSPERMIA (FIGURE 21-4)

1. When no sperm are found on semen analysis, the specimen should be centrifuged and further examined to confirm the finding. In addition, **collection error** and/or retrograde ejaculation must be ruled out as causes of azoospermia. If **retrograde ejaculation** is identified by the finding of sperm in the urine (more than 10 to 15 sperm per high-power field), treatment can be initiated with sympathomimetic agents to promote antegrade ejaculation. Alternatively, sperm can be retrieved from the bladder, processed, and used for IUI.
2. The results of the fructose test and gonadotropin levels determine what additional evaluation and treatment is necessary.
    a. The LH, FSH, and testosterone levels can differentiate **primary testicular failure** from secondary testicular failure caused by either pituitary or hypothalamic dysfunction.
    b. A serum **FSH more than three times normal** along with atrophic testicles on physical examination constitutes a **medical biopsy** of the testis and indicates severe testicular failure. **However, it does not mean that no sperm are in the testis because one half of men can have low numbers of testicular sperm on more extensive evaluation.** However, this finding obviates the need for a surgical biopsy to rule out obstruction. Sperm found in these men can be used with IVF/ICSI by testicular sperm extraction techniques (TESE).

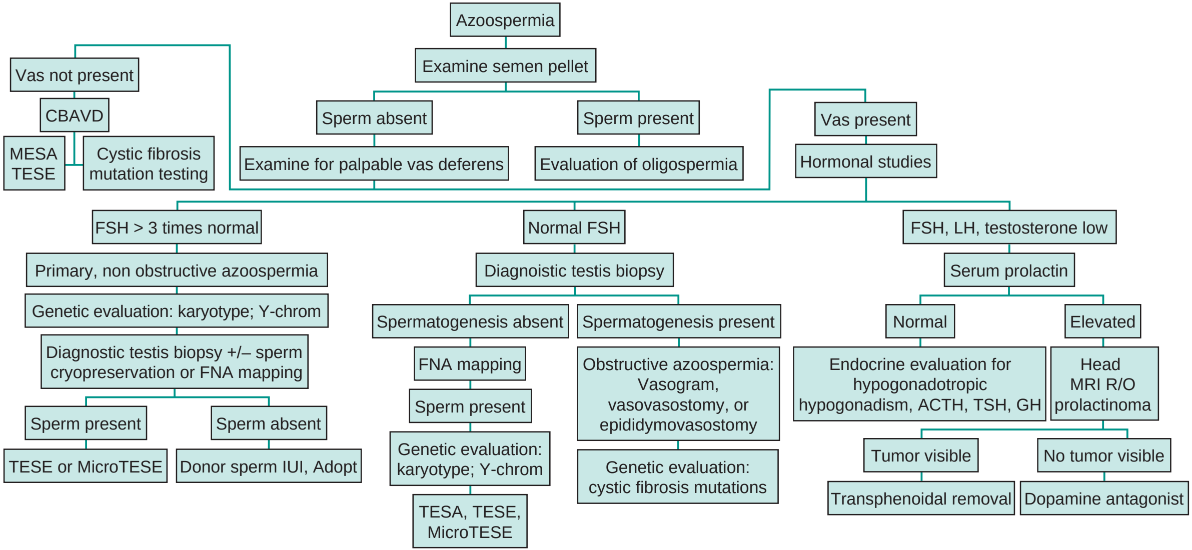
Azoospermia
Examine semen pellet
Vas not present
CBAVD
MESA TESE
Cystic fibrosis mutation testing
Sperm absent
Sperm present
Examine for palpable vas deferens
Evaluation of oligospermia
Vas present
Hormonal studies
FSH > 3 times normal
Normal FSH
FSH, LH, testosterone low
Primary, non obstructive azoospermia
Diagnoistic testis biopsy
Serum prolactin
Genetic evaluation: karyotype; Y-chrom
Spermatogenesis absent
Spermatogenesis present
Normal
Elevated
Diagnostic testis biopsy +/– sperm cryopreservation or FNA mapping
FNA mapping
Obstructive azoospermia: Vasogram, vasovasostomy, or epididymovasostomy
Endocrine evaluation for hypogonadotropic hypogonadism, ACTH, TSH, GH
Head MRI R/O prolactinoma
Sperm present
Sperm absent
Sperm present
Tumor visible
No tumor visible
TESE or MicroTESE
Donor sperm IUI, Adopt
Genetic evaluation: karyotype; Y-chrom
Genetic evaluation: cystic fibrosis mutations
Transphenoidal removal
Dopamine antagonist
TESA, TESE, MicroTESE

FIGURE 21-4 Algorithm for the azoospermic patient. *CBAVD,* Congenital bilateral absence of the vas deferens; *MESA,* microscopic epididymal sperm aspiration; *TESE,* testicular sperm extraction; *FNA,* fine-needle aspiration; *Y-chrom,* Y chromosome microdeletion; *FSH,* follicle-stimulating hormone; *LH,* leutinizing hormone; *ACTH,* adrenocorticotropic hormone; *TSH,* thyroid-stimulating hormone; *GH,* growth hormone; *IUI,* intrauterine insemination.

3. After ruling out a major endocrine abnormality, the major differential diagnosis is **ductal obstruction** or **testicular failure**.

   Consider female-factor infertility

   a. Negative semen fructose test: Three possibilities exist in the azoospermic patient with normal hormone studies and a negative fructose test. These include CAVD and seminal vesicles, bilateral ejaculatory duct obstruction and, rarely, **seminal vesicle dysfunction** similar to bladder myopathy. The treatment of CAVD is direct sperm aspiration from the epididymal remnant or testicle. The sperm are then processed and used in combination with IVF and ICSI. Ejaculatory duct obstruction is managed by transurethral resection of the ejaculatory ducts or by unroofing midline cysts.
   b. Positive fructose test: A positive fructose test usually rules out complete obstruction of the ejaculatory ducts and severe dysfunction of the seminal vesicles but does not assess the patency of the ductal system from the level of the testis to the ejaculatory ducts. Therefore a positive fructose test in azoospermia does not differentiate between proximal ductal obstruction and testicular failure.
   c. Testicular biopsy: A testicular biopsy is important in the azoospermic patient with normal hormones and normal-sized testes with fructose in the ejaculate. The microscopic examination of the biopsy will indicate whether spermatogenesis is progressing normally. With the advent of IVF and ICSI, sperm found on testicular biopsy can also be cryopreserved for future use.
   d. If the testicular biopsy indicates active and complete spermatogenesis, scrotal exploration and vasography are indicated. A **vasogram** is performed by injecting contrast material through one vas deferens to determine patency to the prostatic urethra. If patency is demonstrated, then exploration of the epididymis is undertaken to localize the site of obstruction. Fluid within the vas deferens lumen at **vasotomy** should also be examined microscopically to determine if sperm are present or absent. A microscopic **vasoepididymostomy** is necessary to correct epididymal obstruction. If no spermatozoa are detected in the tubules of the epididymis during this exploration, then intratesticular ductal obstruction may be present. Because these cases are

difficult to correct, IVF and ICSI with testicular sperm are recommended.

4. Vasectomy is one cause of azoospermia amendable to surgical repair with microsurgery (Figure 21-5). It is well established that surgeon experience and optical magnification improve

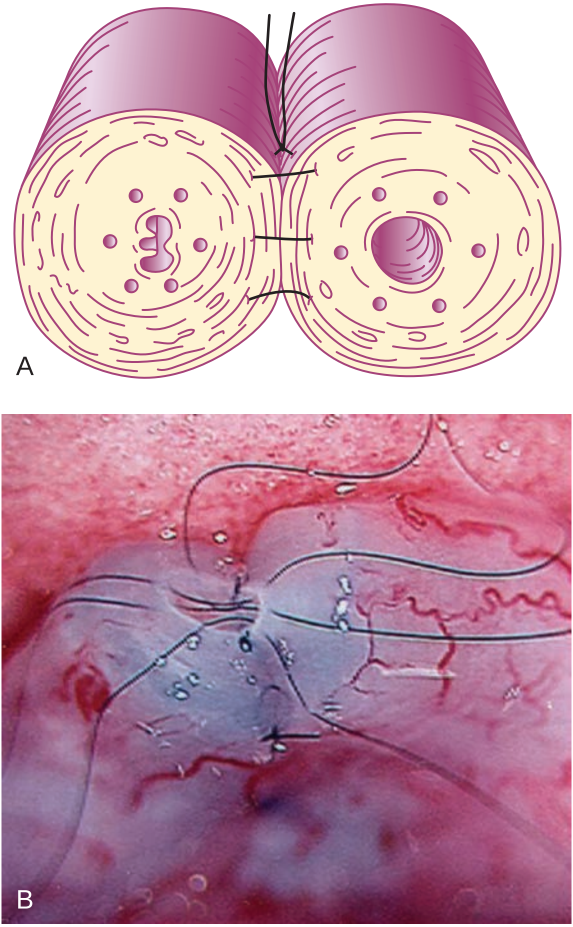

FIGURE 21-5 Vasectomy reversal surgery is performed with intraoperative microscopy. **(A)** Schematic showing reconnection of two vasal ends. **(B)** Intraoperative photo of surgical anastomosis before inner sutures are tied.

outcomes after vasectomy reversal. In experienced hands, **a return of motile sperm to the ejaculate is possible in 90% to 99% of cases of vasovasostomy, with pregnancy rates of 35% to 60%, depending on partner fertility potential.** In older vasectomies, it is often necessary to perform **vasoepididymostomy** for secondary epididymal obstruction that is acquired from prolonged obstruction after vasectomy.

## MULTIPLE ABNORMAL PARAMETERS ON THE SEMEN ANALYSIS

1. Diffuse abnormalities of all or many of the seminal parameters are the most common pathologic pattern identified (55%). Determination of the LH, FSH, and testosterone levels rule out an endocrine abnormality.
2. Stress, infections, and other environmental factors such as hot tubs or bath, drugs, and toxin exposures may produce a transient abnormality of all seminal parameters. Therefore, when other factors are not identified by the history or physical examination, it may be prudent to follow patients for 3 to 6 months to assess self-correction. If spontaneous correction has not occurred, nonspecific therapy can be instituted as discussed below. Couples can also be offered assisted reproductive technology (ART; IUI, IVF).
3. Varicoceles
    a. A **varicocele** is defined as **dilated, varicose internal spermatic veins** producing fullness, dilatation, and **poor drainage of the pampiniform plexus.** A varicocele is found in **15%** of males in the general population and in **35% to 40% of men presenting with infertility** problems and results in abnormal semen parameters.
    b. Varicoceles are **classified according to size as either large (grade III), medium (grade II), or small (grade I).** Large varicoceles can be seen as a "bag of worms" under the scrotal skin. Medium varicoceles are readily detected by palpation, especially on standing. Small varicoceles can only be identified by feeling an impulse in the scrotum with the Valsalva maneuver or by feeling a difference in the size and fullness of the spermatic cord when the patient moves from the standing to the supine position. The majority (90%) of varicoceles occurs on the left side, and the remainder is bilateral. Isolated right varicoceles suggest intraabdominal

or retroperitoneal pathology and merit abdominal and pelvic imaging.

  c. The exact mechanism through which the varicocele exerts a detrimental effect on fertility is unclear; the leading theory is that it leads to **increased intrascrotal temperature** through retrograde venous blood flow. It characteristically decreases normal sperm morphology with an increase in immature and tapered sperm forms (***stress pattern***)**.** Decreased sperm motility and varying degrees of oligospermia also may exist.
  d. Varicocele treatment involves surgical ligation or transvenous angiographic identification and embolization of involved internal spermatic veins. The usual surgical approach is **retroperitoneal, inguinal, or subinguinal** with ligation of the internal spermatic and collateral veins. Laparoscopy is often used to treat bilateral varicoceles. For venous occlusion, a variety of techniques is used, including sclerosing solutions, balloons, and stainless-steel coils.
  e. Results of varicocele ligation from published series indicate that **semen analysis improvement occurs in 70%** of cases, with an associated **40% pregnancy rate.** With baseline sperm counts greater than 10 million sperm per milliliter, pregnancy rates are significantly higher than if the initial counts are lower. Generally, varicocele recurrence rates are lower with surgical (5%) versus angiographic (20%) treatments. **Pregnancies generally occur at a mean of 7 to 8 months following varicocelectomy.**

## ISOLATED ABNORMAL PARAMETER ON SEMEN ANALYSIS (FIGURE 21-6)

1. Abnormal semen volume
    a. Large ejaculate volume: A volume greater than 5.5 mL may result in dilution of the spermatozoa and poor cervical placement of seminal fluid during intercourse. Mechanical concentration of the spermatozoa and IUI may overcome this issue.
    b. Absent or low ejaculate volume (Figure 21-7). Once a collection abnormality has been ruled out, it is essential to consider **retrograde ejaculation, infection of the accessory sex glands, or endocrine dysfunction (low testosterone).**

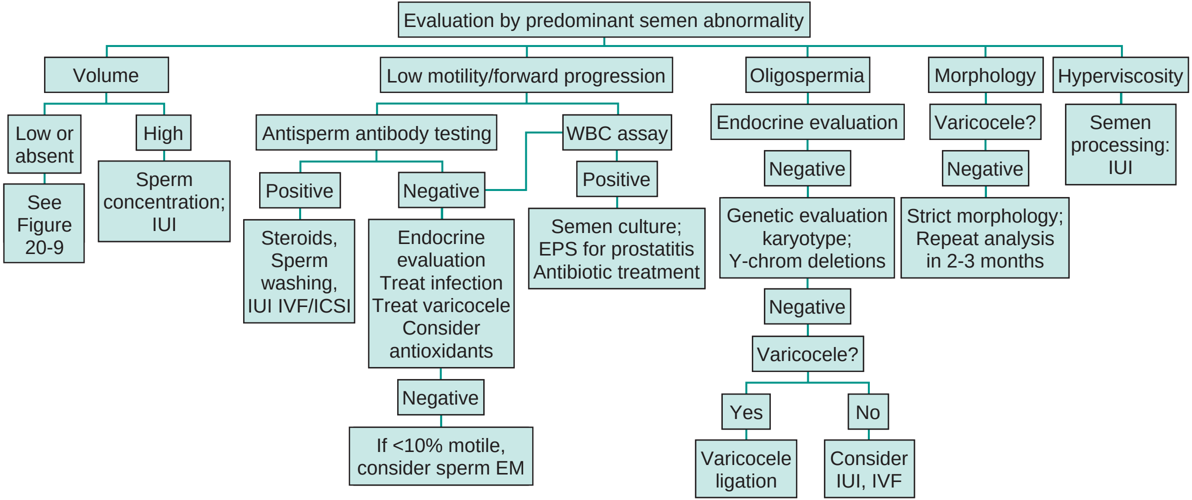
Evaluation by predominant semen abnormality
Volume
Low or absent
See Figure 20-9
High
Sperm concentration; IUI
Low motility/forward progression
Antisperm antibody testing
Positive
Steroids, Sperm washing, IUI IVF/ICSI
Negative
Endocrine evaluation Treat infection Treat varicocele Consider antioxidants
Negative
If <10% motile, consider sperm EM
WBC assay
Positive
Semen culture; EPS for prostatitis Antibiotic treatment
Oligospermia
Endocrine evaluation
Negative
Genetic evaluation karyotype; Y-chrom deletions
Negative
Varicocele?
Yes
Varicocele ligation
No
Consider IUI, IVF
Morphology
Varicocele?
Negative
Strict morphology; Repeat analysis in 2-3 months
Hyperviscosity
Semen processing: IUI

FIGURE 21-6 Algorithm for the patient with a single predominant abnormality on semen analysis. *IUI,* Intrauterine insemination; *WBC,* white blood cell; *EM,* electron microscopy; *IVF/ICSI,* in vitro fertilization with intracytoplasmic sperm injection.

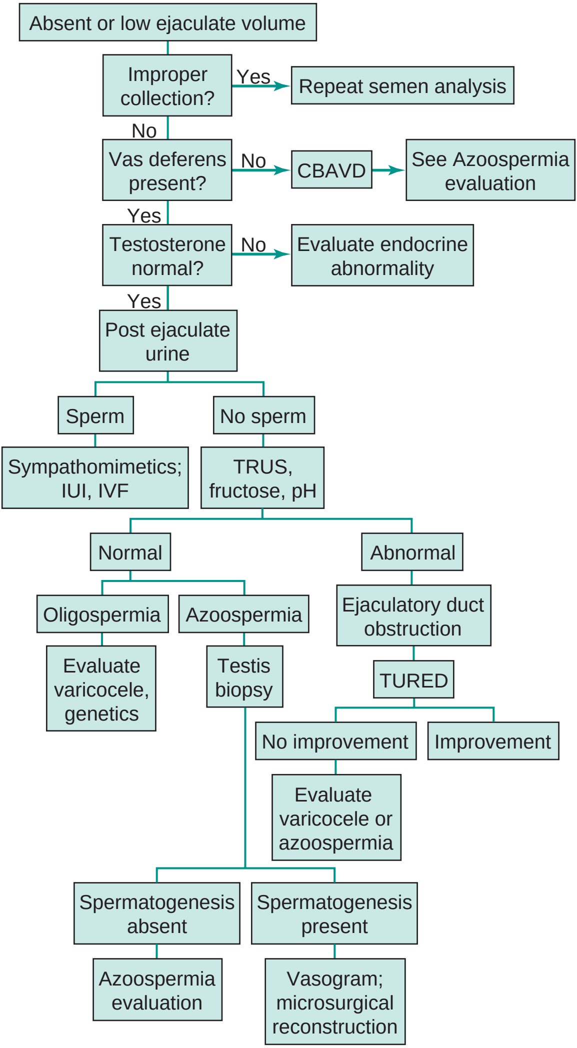

FIGURE 21-7 Algorithm for patients with absent or low-volume (less than 1.5 mL) ejaculate. *CBAVD,* Congenital bilateral absence of the vas deferens; *IUI,* intrauterine insemination; *IVF,* in vitro fertilization; *TRUS,* transrectal ultrasound; *TURED,* transurethral resection of the ejaculatory ducts.

The presence of retrograde ejaculation is confirmed by the finding of large quantities of spermatozoa in the postejaculatory urine sample (greater than 15 sperm per HPF). Sympathomimetic drugs with alpha-adrenergic activity can reverse this issue in one third of patients, and generally in those without scar tissue at the bladder neck from prior surgery. In others, it may be necessary to obtain, wash, and inseminate (IUI) sperm collected from the postejaculate urine sample. Endocrine abnormalities and infections are treated with the appropriate hormones and antibiotics.

2. Hyperviscosity: Problems with hyperviscous semen are rare and may reflect enzymatic imbalance in semen. Mechanical disruption of the sample in the laboratory to decrease viscosity, followed by IUI, is useful in this situation.
3. Decreased motility and forward progression (asthenospermia)
    a. This is the most common isolated abnormality found in semen and can be due to endocrine dysfunction, infection of accessory glands, varicocele, epididymal dysfunction, genetics, reactive oxygen species (oxidants), or environmental exposures. Specific therapy is available for some of these problems. Empirical treatment with antioxidant supplements (vitamins A, C and E, zinc, and folate) may also be tried.
    b. Sperm motility may also be adversely affected by **antisperm antibodies** that agglutinate or immobilize sperm. Special sperm tests can determine levels of antisperm antibodies in semen. Treatments are available for antibodies, including IUI, IVF, ICSI, and treatment of the male with systemic steroids for 6 to 9 months. The latter therapy has been associated with decreased antibody levels but not necessarily increased natural pregnancy rates.
4. Oligospermia
    a. Decreased sperm numbers may be secondary to endocrine dysfunction, genetic or idiopathic conditions, or unilateral obstruction. Occasionally, the absolute number of sperm is relatively normal, but the number of sperm per milliliter may appear low because of large ejaculate volume. **With sperm densities less than 5 X $10^6$/mL, karyotype analysis and Y chromosome microdeletions should be evaluated** (see Figure 21-e4).

   b. In general, two treatments exist for oligospermia. One attempts to stimulate the testes with drugs to increase the output of spermatozoa (see the next section on idiopathic infertility). Alternatively, with advances in assisted reproduction, spermatozoa can be concentrated for use with IUI. In addition, IVF and ICSI are available when simpler approaches fail.

5. Abnormal morphology: An isolated problem with morphology is unusual. This may result from gonadotoxic exposures (e.g., tobacco), systemic illness, fevers, varicocele, or idiopathic causes. Reversing the toxic exposure can improve sperm morphology.

## EMPIRICAL TREATMENT OF IDIOPATHIC MALE-FACTOR INFERTILITY

1. Second only to those with varicoceles, **idiopathic male infertility** is the next largest group of infertility patients. Essentially, idiopathic infertility refers to men who have an abnormal semen parameter or parameters on the semen analyses with a normal history, physical examination, and screening hormone analysis. The etiology of the abnormal semen quality is unclear and probably reflects our incomplete knowledge of the genetics of spermatogenesis and sperm maturation. Many of these cases will likely be seen to have genetic etiologies in the future.
2. Nonpharmacologic treatments. Various nonpharmacologic treatments have been suggested, but their efficacy has not been rigorously demonstrated. These include:
   a. Vitamins and diet: Changes in dietary habits and vitamin supplements have been associated with improved semen quality and fertility. Antioxidant therapy has been shown to increase motility of in vitro isolated sperm, but a similar treatment of men with unexplained severe asthenospermia did not reliably improve motility in a large, randomized study. This therapy may be beneficial for smokers to reduce the oxidative effects on sperm.
   b. Changing from jockey shorts to **boxer shorts:** A recent study has refuted the idiom that a switch from jockey to boxer shorts improves spermatogenesis and semen parameters.
   c. Prostatic massage
   d. Antibiotics for occult infection

   e. Varicocelectomy for the occult or **subclinical varicocele:** Three randomized, controlled clinical trials demonstrated no benefit to varicocelectomy for nonpalpable, ultrasound-detected lesions.
3. Drug therapy for idiopathic infertility
   a. The use of **human menopausal gonadotropin** (**hMG**) or **recombinant FSH, human chorionic gonadotropin** (**hCG,** essentially LH), or the combination of FSH and hCG does not significantly improve sperm counts or fertility with idaiopathic infertility. GnRH therapy, when given in a pulsatile fashion, has the potential to raise LH and FSH levels, but its administration is complex and costly.
   b. **Clomiphene citrate** is an antiestrogen that has been used nonspecifically for idiopathic infertility for 40 years. As a **selective estrogen receptor modulator** (**SERM**)**,** this medication blocks the negative feedback of **estradiol** on the hypothalamic-pituitary axis, resulting in increased LH and FSH levels. Overall improvement in the semen analysis is observed in half of patients, and pregnancies occur in 25% to 30% of patients in uncontrolled studies. Men with low-normal testosterone and FSH levels, indicative of mild central hypogonadism, respond best to this therapy.
   c. **Tamoxifen** is also an antiestrogen. This agent, however, lacks the estrogenic activities of clomiphene and may provide equal efficacy.
   d. **Aromatase inhibitors** block the conversion of testosterone to estrogens in men. They may be useful in oligospermic or azoospermic men with a **testosterone:estrogen ratio of less than 10:1** to increase sperm yield from the ejaculate or from the testicle with surgical extraction.
   e. **L-carnitine** is found in high concentrations in the normal epididymis and is postulated to be important for sperm motility. Oral L-carnitine is widely available, and there is early evidence that some men with low motility, especially those with varicoceles, will show improvement.

## ASSISTED REPRODUCTIVE TECHNOLOGY

1. ART can improve conception rates by bypassing many or all of the barriers associated with normal fertilization. The simplest techniques involve sperm processing and insemination of the female; more sophisticated ones involve manipulation of

the sperm and ova extracorporeally. Fertilization with these procedures can occur in vitro or in vivo.

2. Semen processing is used as an isolated procedure or in conjunction with oocyte processing. **Sperm washing, swim-ups, sedimentation, and gradient centrifugations** are common ways to remove seminal plasma and leukocytes and to select for and concentrate highly motile sperm. With these procedures, fewer sperm than normal are needed because they are placed higher within the female reproductive tract than an ejaculate during intercourse.
3. **IUI** is a common treatment for male-factor infertility. In this technique, a small catheter is used to inject processed sperm through the cervix and into the uterine cavity. By bypassing the cervical mucus, more motile sperm can progress to the fallopian tubes where normal fertilization occurs. Indications for IUI include male infertility caused by mechanical or anatomical problems (e.g., ED, hypospadias), low semen quality, and cervical mucus problems. **Usually, more than 5 million motile sperm are required for a successful IUI. Pregnancy rates are variable with these techniques, but average 30% to 35% in couples who try three to four times.**
4. **IVF**, first introduced in 1978, was developed to manage fallopian tube obstruction. It is now used routinely for male factor infertility (Figure 21-8). Female partners undergo ovarian hyperstimulation to induce the maturation of multiple oocytes which are then harvested ultrasonographically, just prior to ovulation. Processed semen and recovered oocytes are mixed in vitro. If fertilization occurs, embryos are placed back into the uterus transcervically. Usually only 20% to 30% of replaced embryos survive and become clinical pregnancies. Depending on the cause of infertility, and the number of embryos replaced, pregnancy rates can approach 40% to 50% per IVF attempt.
5. In gamete intrafallopian transfer (**GIFT**), sperm and oocytes are placed into the fallopian tubes prior to fertilization. This is done in lieu of uterine placement with the hope that higher pregnancy rates will be achieved with more physiologic placement of gametes. Because GIFT does not improve the fertilizing capacity of sperm, it has no benefit over IVF in male-factor infertility. Given the recent success of IVF and ICSI, tubal transfers constitute fewer than 2% of ART cases.

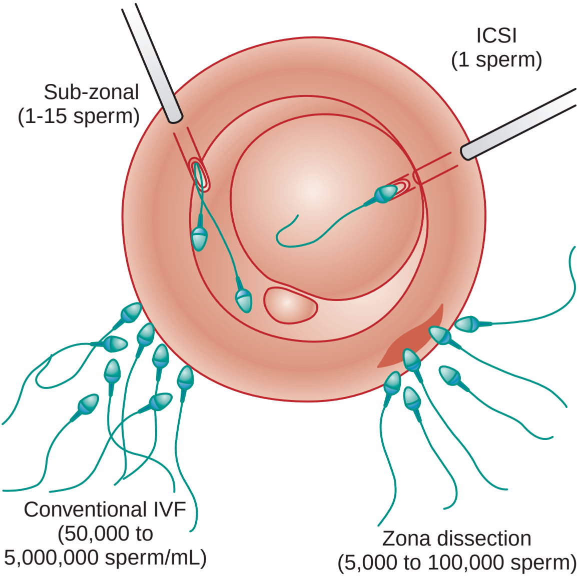

FIGURE 21-8 Available methods of in vitro fertilization (IVF) with micromanipulation of gametes. Among the techniques illustrated, IVF and intracytoplasmic sperm injection (ICSI) are currently the most commonly used.

6. Micromanipulation (see Figure 21-6). Sperm and oocyte micromanipulation by **ICSI has become the mainstay of addressing the poor fertilizing capacity of sperm often seen in male infertility.** By injecting a single sperm directly into an oocyte, multiple barriers of fertilization are bypassed and success rates (when compared to standard IVF) are greatly improved. Pregnancy rates of 40% to 50% have been obtained using this technique even in the most severe cases of male infertility. In addition, not only ejaculated sperm but sperm retrieved from the male reproductive tract are capable of pregnancy with ICSI. **Vasal, epididymal, and even testicular sperm, from both obstructed and unobstructed men, are now routinely used with IVF and ICSI.**
7. **IVF with ICSI** should not be performed without **karyotype analysis on both partners.** Despite its great success, concerns remain with ICSI.

a. **Multiple gestations occur in 35% of pregnancies compared to 1% to 2% of naturally conceived pregnancies.** Multiple gestations are associated with lower birth weights, higher overall complication rates, and increased learning disabilities relative to singletons. In addition, the **delivery costs** associated with managing multiple, often premature, gestations are at least **10 to 20 times higher** than that associated with the singleton deliveries. Among respectable ART programs, the trend is to transfer as few embryos back as possible to reduce multiple gestations.

b. **ICSI bypasses many mechanisms of natural selection such that many men who would not be able to conceive under normal circumstances are now able to father children.** Although overall rates of **major birth defects** (**3.3%**) associated with IVF and ICSI may be similar to intercourse, there is concern about elevated risks of specific malformations, including **hypospadias**, with this technology. In addition, concerns exist regarding possible **developmental issues**. There is a significant **increase in sex chromosomal abnormalities** among ICSI offspring (**0.8% versus 0.2% naturally**) that is likely attributable to the chromosomal status of the fathers rather than to the technique itself. As previously mentioned, from 5% to 8% of men with severe oligospermia have deletions in the AZF region of the Y chromosome. It has been shown conclusively that these genetic deletions are passed to the male offspring produced by these fathers through IVF/ICSI.

c. More recently, concerns have arisen regarding whether **rare imprinting diseases such as Beckwith-Wiedemann syndrome and Angelman syndrome** are increased in children conceived with ICSI. For these reasons, genetic counseling is recommended for all couples considering IVF-ICSI.

8. Preimplantation genetic diagnosis (**PGD**) is now possible by sampling a single cell from the developing embryo in vitro and performing fluorescent in situ hybridization (FISH), single-cell polymerase chain reaction (PCR), or comparative genomic hybridization (CGH) to **examine for aneuploidy, chromosomal translocations, or specific diseases caused by point mutations.** Current indications for PGD include lethal disease prevention and screening in advanced maternal age couples.

## Conclusion

Our knowledge of testis development, testis stem cells, and sperm production are rapidly evolving. As the chromosomal and molecular mechanisms that underlie sperm production are further elucidated, fewer male patients with infertility will have undefined etiologies. Concurrently, fast-paced ARTs now allow us to bypass many natural selection barriers that had been present throughout evolution. As a consequence, the study of human reproduction is more important than ever to allow us to understand how our evolution is being altered by technology.

Despite these advances in technology, classical treatments for male infertility still remain cost effective. Indeed, a properly conducted male-factor infertility evaluation has immense value on several levels: (1) it can identify treatable diseases that underlie the infertility, (2) it can identify those individuals who might be at risk for future diseases such as prostate and testis cancer, and (3) it can cure, and not simply bypass, the infertility.

### CLINICAL PEARLS

1. Semen quality and male fertility are reasonable mirrors of overall health of an individual. Likewise, when semen quality is impaired, efforts should be made during the infertility evaluation to find out why.
2. Classic medical treatments for male infertility, such as repair of blockages and varicoceles, continue to be cost-effective when compared to assisted reproduction.
3. Dramatically low or zero sperm counts that are genetic in origin do not generally respond to classical medical and surgical therapies for male infertility. Such cases are excellent candidates for assisted reproduction.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Embryologically, the vas deferens and body of the epididymis are derived from what developmental structure?*
   a. *Mullerian ducts*
   b. *Wolffian ducts*
   c. *Urogenital ridge*
   d. *Gubernaculum testis*
2. *The vast majority of the fluid in the male ejaculate is derived from the:*
   a. *Epididymides*
   b. *Ejaculatory ducts*
   c. *Seminal vesicles*
   d. *Testicles*
   e. *Vas deferens*
3. *The most common and correctable identifiable problem causing male infertility is:*
   a. *Infection*
   b. *Obstruction*
   c. *Gonadotoxin exposure*
   d. *Varicocele*
4. *A 25-year-old bodybuilder eschews the merits of "natural" bodybuilding and cycles and stacks injectable anabolic steroids regularly to maximize muscle bulk. His fertility potential would be expected to be:*
   a. *Normal because exogenous testosterone does not impair production of endogenous testosterone*
   b. *Low because exogenous testosterone stimulates pituitary production of FSH and LH*
   c. *Low because exogenous testosterone inhibits pituitary production of FSH and LH*
   d. *Low because exogenous testosterone is not as potent as endogenous testosterone at nurturing spermatogenesis*
   e. *Normal because intratesticular testosterone concentrations are 50 times higher than serum levels, whether or not the blood contains exogenous testosterone*
5. *The role of PSA in the ejaculate is:*
   a. *To coagulate the ejaculate*
   b. *To serve as a marker for prostate cancer*
   c. *To serve as a liquefaction factor*
   d. *To give semen its characteristic odor*

## SUGGESTED READINGS

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## CHAPTER 22

# Disorders of the Adrenal Gland

Alexander Kutikov, MD, FACS

Urologists care for patients with adrenal disorders principally from the surgical perspective. This chapter provides an overview of adrenal pathophysiology and addresses tactics used in urologic clinical practice to assess and manage surgical adrenal disease.

## Adrenal Anatomy

### OVERVIEW

1. Adrenals, each weighing approximately 4 to 5 g and measuring 5 x 3 x 1 cm, are positioned in the retroperitoneum within Gerota fascia anterior and superomedial to each kidney.
2. The right adrenal, described as triangular, lies posterior and lateral to the inferior vena cava (IVC) and contacts the liver anteriorly.
3. The smaller left gland tends to be semilunar and is intimately related to the upper pole of the left kidney. Anterior to the left adrenal lies the tail of the pancreas and the splenic artery. The diaphragm borders both adrenals posteriorly.

### VASCULATURE

Blood flow through the adrenals is substantial, given the endocrine function of the glands. Understanding adrenal vasculature is critical for safe retroperitoneal surgery. The venous drainage of the right gland differs from that of the left, and the surgeon must be aware of this fact.

#### Arterial Supply

1. No one dominant artery supplies either adrenal.
2. Small vessels enter the glands from three main sources:
    a. Inferior phrenic artery: superior adrenal arteries, majority of blood supply

   b. Aorta at the level of the superior mesenteric artery (SMA): middle adrenal arteries
   c. Renal artery: inferior adrenal arteries
3. Arteries rapidly branch, and as many as 60 separate vessels may penetrate the adrenal capsule in a stellate fashion.

## Venous Drainage

### *Right Adrenal Vein*

1. Short vessel drains directly into the posterior aspect of the IVC.
2. If torn during dissection, can result in life-threatening bleeding and has been called "the vein of death".
3. In some patients, joins with a right hepatic vein prior to entering the vena cava.
4. Accessory right adrenal vein(s) occasionally may be present.

### *Left Adrenal Vein*

1. The left adrenal vein is substantially longer than the right.
2. Drains directly into the left renal vein.
3. Usually joins with the inferior phrenic vein at some point in its course.
4. As on the right, accessory veins may be present.

## HISTOLOGIC STRUCTURE

The adrenal gland, surrounded by a capsule, is composed of a yellowish cortex and a red-to-grey medulla. The cortex stems from the mesoderm, and the medulla originates from the neuroectoderm.

1. Cortex: The adult cortex is composed of three distinct concentric regions and comprises 80% of total adrenal weight.
   a. Zona glomerulosa: mineralocorticoid production (outer zone)
   b. Zona fasciculata: glucocorticoid production (middle zone)
   c. Zona reticularis: androgen production (inner zone)
2. Medulla: This lies in the center of the gland beneath the zona reticularis. Rich in chromaffin cells (named so because precipitate chromium salts), the medulla produces catecholamines such as epinephrine, norepinephrine, and dopamine.

At birth, the adrenal is of adult size. The gland rapidly begins to involute following delivery, losing tissue from a region known as the fetal cortex and weighing only 50% of its weight at birth when the child is 1 month of age.

# Adrenal Physiology

## ADRENAL CORTEX PHYSIOLOGY

Each of the three zones of the cortex contains different enzymes along the three major synthetic pathways, resulting in three different classes of steroid hormones produced in each zone (Figure 22-1).

1. **Zona glomerulosa** is the site for daily production of up to 150 mg of aldosterone, the major mineralocorticoid in humans. Aldosterone is a pivotal player in the renin-angiotensin system and participates in control of the body's fluid and electrolyte equilibrium.

2. **Zona fasciculata** is the site of glucocorticoid production and excretes up to 30 mg of cortisol each day. Unless pathology is present, cortisol secretion is under tight control of pituitary adrenocorticotropic hormone (ACTH) through the hypothalamic-pituitary-adrenal axis. Cortisol, essential for life, modulates numerous complex physiologic pathways that include metabolism, immunity, maintenance of intravascular volume, and regulation of blood pressure (BP).

3. **Zona reticularis,** the innermost zone of the adrenal cortex, is the source of adrenal androgens. The major sex steroid hormone of the adrenal is dehydroepiandrosterone (DHEA). In normal physiologic states, these hormones have little influence; however, excess production of these agents can lead to profound consequences (e.g., congenital adrenal hyperplasia [CAH]).

## ADRENAL MEDULLA PHYSIOLOGY

The adrenal medulla is an integral part of the autonomic nervous system and the fight-or-flight response. Chromaffin cells, innervated by preganglionic sympathetic fibers, secrete norepinephrine, epinephrine, and dopamine.

# Adrenal Disorders

## INCREASED ADRENAL FUNCTION

### Cushing syndrome, Conn syndrome, and pheochromocytoma

1. **Cushing syndrome:** A condition of excess circulating glucocorticoid
   a. Signs and symptoms arise from chronic hypercortisolism.

The adrenal cortex and the adrenal medulla not only have distinct embryologic origins but also function as independent hormone-producing units. With cholesterol-derivative pregnenolone as substrate, numerous enzymes of the adrenal cortex catalyze synthesis of essential hormonal agents.

Steroid hormones do not bind to receptors on cellular membranes but instead modulate gene transcription by uniting with their receptors within the cell and then binding directly to DNA as the receptor-hormone complex.

This hormone, through its action on the distal convoluted tubule of the kidney, promotes sodium (and therefore fluid) retention and potassium and proton excretion. Secretion of aldosterone is directly influenced by the body's angiotensin II and potassium levels. It is important to note that the hypothalamic-pituitary-adrenal axis plays little role in aldosterone secretion. Indeed, the zona glomerulosa is the only region of the adrenal cortex that does not atrophy following loss of pituitary function.

Androstenedione and sulfated form of DHEA (DHEA-S) are also formed and, along with DHEA, act as weak androgens.

1. Liver rapidly metabolizes catecholamines that are released by the medulla. This breakdown is catalyzed by:
    a. Catechol O-methyltransferase (COMT)
    b. Monoamine oxidase (MAO)
2. Catecholamine metabolites and small amounts of norepinephrine are excreted in the urine. The major metabolites include:
    a. Metanephrine
    b. Normetanephrine
    c. Vanillylmandelic acid (VMA)

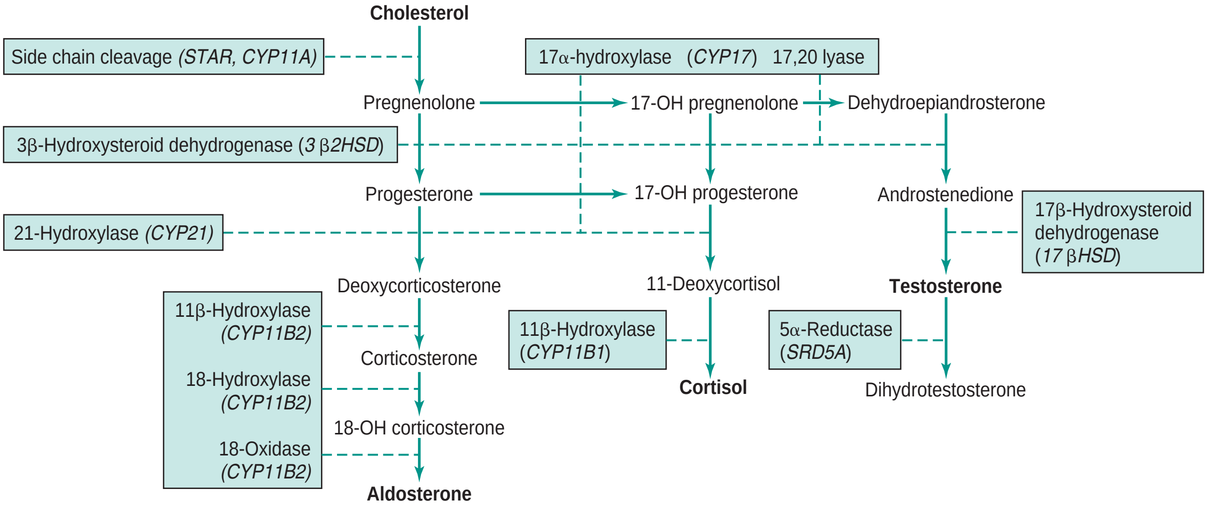

FIGURE 22-1 Cholesterol-steroid biosynthesis pathway. Enzymes are listed in boxes and genes in parentheses. (From Hyun G, Kolon TF: A practical approach to intersex in the newborn period, *Urol Clin North Am* 31:435–443, 2004.)

b. Causes of excess cortisol: Only a minority arise from the adrenal gland.
    1) Primary adrenal hypercortisolism is a rare cause of Cushing syndrome.
        a) Adrenal adenoma and adrenal carcinoma cause approximately the same number of cases of Cushing syndrome per year (approximately 10% each).
        b) Bilateral micronodular hyperplasia is a rare cause of primary adrenal hypercortisolism.
        c) Bilateral ACTH-independent macronodular hyperplasia: Adrenals weigh up to 500 g each; this is extremely rare.
    2) Nonadrenal causes of Cushing syndrome
        a) Iatrogenic steroid administration is a very common cause of Cushing syndrome.
        b) **ACTH-producing pituitary tumors** (Cushing disease) are responsible for up to 70% of cases of Cushing syndrome. Adrenal glands are hyperplastic (6 to 12 g) but less so than in nonpituitary ectopic ACTH cases.
        c) **Ectopic ACTH** is responsible for up to 15% of cases of Cushing syndrome. Half are caused by paraneoplastic action of small-cell lung cancer. Other malignancies such as carcinoid and pancreatic and thyroid tumors can also be culprits. Adrenal glands become extremely hyperplastic (12 to 30 g).
        d) **Ectopic corticotropin-releasing hormone (CRH)** is extremely rare.

c. Comprehensive patient evaluation for Cushing syndrome is complex and is beyond the scope of this text. Diagnostic strategies as they relate to urologic practice, however, are discussed later in this chapter (see Evaluation of Adrenal Pathology in Urologic Practice).

2. **Conn syndrome:** Primary hyperaldosteronism
    a. Signs and symptoms stem from physiologic action of aldosterone to promote renal sodium reabsorption by opening sodium channels in cells of the renal cortical collecting-system lumen.
        1) Hypertension
            a) Results from intravascular volume expansion
            b) Mean BPs of 180/110 mm Hg in patients with aldosterone-secreting adenomas and 160/100 mm Hg in those with idiopathic bilateral adrenal hyperplasia

a. Endothelial cysts are most common (approximately 40%).
    1) Benign
    2) Calcifications are common and do not suggest malignancy.
b. Pseudocysts are the second most common adrenal cystic lesion.
    1) Lack epithelial lining
    2) Arise from encapsulation of foci of previous adrenal hemorrhage
    3) Can get very large and cause symptoms, otherwise benign
c. Cystic lymphangiomas are benign.
d. Echinococcal cysts can be found in the adrenal.
e. Epithelial cysts are the most common cystic lesion in the kidney but very rare in the adrenal gland.

    - c) Renin levels are very low.
    - d) Normotensive patients are extremely rare.
  - 2) Hypokalemia
    - a) Not present in all patients
    - b) Balanced by the renal potassium-sparing effects of hypokalemia itself; can be exacerbated by sodium loading
    - c) Can result in polyuria, polydipsia, and muscle weakness
  - 3) Metabolic alkalosis is caused by potassium-induced $H^+$ wasting.
  - 4) Other metabolic abnormalities include mild hypernatremia (approximately 145 mEq/L) and hypomagnesemia.
- b. Causes of Conn syndrome
  - 1) Adrenal adenoma
    - a) Cause of up to 70% of cases of primary hyperaldosteronism
    - b) Surgical disease
      - i) BP falls and potassium level returns to normal in almost all patients following adrenalectomy. A lesser degree of hypertension can linger in up to 70% of patients. This may be due to many factors, but the urologist should keep in mind that up to 30% of patients with a solitary adrenal mass actually have bilateral adrenal hyperplasia when adrenal vein sampling is performed.
  - 2) Bilateral adrenal hyperplasia
    - a) Idiopathic
      - i) Responsible for 30% to 40% of Conn syndrome
      - ii) Poor response to surgery—a medical disease: Aldosterone receptor blockade is employed.
    - b) Glucocorticoid-suppressible aldosteronism
      - i) Causes less than 1% of Conn syndrome
      - ii) Autosomal dominant
      - iii) Hyperaldosteronism is ACTH dependent and therefore responds to exogenous glucocorticoid administration.
  - 3) Adrenal carcinoma is responsible for less than 1% of primary hyperaldosteronism.

3. **Pheochromocytoma** is a tumor of the adrenal medulla that generates, stores, and secretes catecholamines.

In cases of secondary hyperaldosteronism (usually due to renal artery stenosis or congestive heart failure [CHF]), renin levels are high.

5) Lack of edema is due to what has been called the "aldosterone-escape phenomenon." Despite high mineralocorticoid levels, volume urinary fluid loss quickly equilibrates with intake, and volume expansion is only mild.
6) Other metabolic abnormalities include mild hypernatremia (approximately 145 mEq/L) and hypomagnesemia.
7) Increased cardiac risks: Patients with hyperaldosteronism have higher rates of cardiovascular events independent of hypertension and potassium levels.
    ii) Treatment with preoperative spironolactone has been suggested. Long-term spironolactone or its counterpart eplerenone (lesser binding affinity to androgen and progesterone receptors) is used to treat poor surgical candidates.

c. Evaluation of patients with hyperaldosteronism as it relates to urologic practice is addressed later in this chapter (see Evaluation of Adrenal Pathology in Urologic Practice).

a. Signs and symptoms are a result of epinephrine, norepinephrine, and dopamine release into the bloodstream by neoplastic chromaffin cells.
    1) Classic symptom triad of headache, palpitations, and diaphoresis
    2) Paroxysmal hypertension present in only approximately 50%, whereas other patients behave identically to those with essential hypertension.
    3) Orthostatic hypotension (result of hypovolemia), papilledema, weight loss, leukocytosis, polycythemia, hyperglycemia, and cardiovascular complications have all been associated with pheochromocytoma.
    4) Patients with pheochromocytoma as part of a genetic syndrome (von Hippel-Lindau [VHL], multiple endocrine neoplasia type 2 [MEN2], and neurofibromatosis type 1 [NF1]) are often asymptomatic and account for 25% of all patients with pheochromocytomas.

b. Clinical characteristics: The rule of 10s (has been repeatedly challenged)
    1) 10% extraadrenal (actually approximately 25%)
    2) Ten percent familial (actually approximately 30%)
    3) Ten percent malignant (actually 5% for adrenal pheochromocytoma and as high as 30% for extraadrenal pheochromocytoma): Pathologic documentation of malignancy is problematic because even benign lesions exhibit capsular penetration and vascular invasion. Histologic features are also nonspecific. Malignancy therefore is defined as *presence of metastasis or invasion of surrounding tissues*.
    4) Ten percent bilateral: This is more common with familial disease. Solitary right-sided tumors are approximately 40% more common than left-sided tumors for unclear reasons and have a threefold higher risk of recurrence.
    5) Ten percent pediatric: Common in familial cases

c. Treatment: Sporadic pheochromocytoma is a surgical disease and should be resected. Partial adrenalectomy has gained popularity in recent years. A multidisciplinary management approach is advised in these patients.
    1) Preoperative catecholamine blockade is paramount for symptomatic patients because life-threatening and even lethal catecholamine surges may occur perioperatively.

  a) Known as paragangliomas
  b) Most common extraadrenal site is the organ of Zuckerkandl (chromaffin bodies at aortic bifurcation)
  c) Can also occur in neck, abdomen, and pelvis, including the bladder
  d) More common with familial disease
  e) Up to tenfold higher risk for recurrence if tumor is extraadrenal
  a) More common in women
  b) More common in extraadrenal disease
  c) Five-year survival 36% to 60%
  d) Radiation, resection of metastases, and chemotherapy can be used to treat aggressive cases.

Treatment strategies for familial cases are more controversial; bilateral disease and recurrence rates are high, yet mortality and morbidity of bilateral adrenalectomy are also significant.

Prior to routine use of prophylactic blockade, surgical mortality was as high as 50%.

   a) Alpha-blockade (or calcium channel blockade) should be initiated 10 to 14 days preoperatively. Some investigators have shown that calcium channel blockade is just as effective and may be safer than alpha-blockade for preoperative management of pheochromocytoma. Doxazosin alpha-blockade and foregoing blockade altogether have been described for asymptomatic patients.
   b) Beta-blockade can be lethal if initiated prior to appropriate alpha-blockade. Beta-blockade is used to treat tachycardia, which may result from alpha-blockade and alpha-blockade-induced arrhythmias. Beta-blockade must be administered with great care because CHF, bradycardia, myocardial depression, asystole, and death have all been documented in patients with pheochromocytoma.
   c) Alpha-methyl-para-tyrosine (metyrosine) administration results in depletion of stored catecholamine because the agent inhibits tyrosine hydroxylase, the rate-limiting enzyme in biosynthesis of catecholamines. The medication should be used with care because side effects are significant.
   d) Intraoperative and postsurgical management: Intraoperative hypertension is generally managed with a nitroprusside drip. Following surgery in patients who required significant blockade, a short intensive care unit (ICU) stay is recommended for monitoring of BP and blood sugar. Aggressive intravenous (IV) fluids and glucose administration are the postoperative routine.

2) Prognosis
   a) Familial, right-sided, and extraadrenal tumors are more likely to recur.
   b) Follow-up should be indefinite because tumors, whether malignant or benign, can recur many years following resection.

## DECREASED ADRENAL FUNCTION

Etiologies for Addison disease (primary adrenal insufficiency), a nonsurgical entity, include:

Phenoxybenzamine 10 mg per os (PO) twice a day (b.i.d.) is started and titrated by daily increases of 10 to 20 mg to a BP of 120/80 mm Hg in a seated position. Mild postural hypotension (systolic blood pressure [SBP] greater than 90 mm Hg in standing position) is tolerated and is a sign of appropriate dosing. In children, 0.2 mg/kg (max 10 mg) daily (QD) dosing should be used with incremental increases by 0.2 mg/kg.

e) Increased salt intake and hydration: After alpha-blockade is initiated, the patient should be encouraged to increase salt intake to increase intravascular volume. Admission at least 24 hours prior to surgery is advisable, so that IV hydration can be administered and appropriate volume status secured.

1. Autoimmune/idiopathic
2. Infectious: Tuberculosis, cytomegalovirus (CMV) adrenalitis in human immunodeficiency virus (HIV) patients, fungal infections, syphilis
3. Infarction and hemorrhage: Meningococcemia (Waterhouse-Friderichsen syndrome), pseudomonal and other infections, coagulopathy, trauma
4. Metastasis: Although metastasis to the adrenals is common, adrenal insufficiency is extremely rare.

## ABNORMAL ADRENAL FUNCTION

Congenital adrenal hyperplasia is addressed in Chapter.

## ADRENAL NEOPLASIA

1. **Adrenal carcinoma** is a rare cancer with a poor prognosis.
    a. Clinical features
        1) Annual incidence is 0.5 to 2 in 1 million (10 times higher in southern Brazil).
        2) Occurs in patients 40 to 50 years of age (most common) and children younger than 5 years of age
        3) Linked to MEN1, Beckwith-Wiedemann, and Li-Fraumeni syndromes
        4) Left tumors are more common.
        5) Sixty percent of tumors are functional.
            a) Approximately 40% is Cushing syndrome.
                i) Cortisol production per unit volume of tumor is low.
                ii) Hypercortisolism results from larger masses.
            b) Approximately 25% is Cushing with virilization; this combination is suggestive of carcinoma because it is almost never seen with adrenal adenomas.
            c) Twenty percent to 30% virilization alone (most common presentation in children)
                i) Serum testosterone, DHEA, DHEA-S are elevated.
                ii) 17-ketosteroids are elevated.
            d) Feminization (approximately 6%) and hyperaldosteronism (2.5%) are rare.
        6) Up to 20% of tumors can have vena caval extension.
        7) Ninety-two percent of adrenal carcinomas are greater than 6 cm at diagnosis. Median size at presentation is 11 cm.
        8) Metastasize to liver, lungs, lymph nodes, and bone

- b. Treatment
  - 1) Surgical resection is the only treatment that impacts survival.
    - a) Local resection is not always curative.
    - b) Debulking is controversial but recommended by most experts.
  - 2) Mitotane
    - a) Drug poisons mitochondria of the adrenal cortical cells.
    - b) Used as primary therapy, adjuvant therapy, and with or without cytotoxic agents for disease recurrence.
    - c) Short-term benefits but not shown to affect survival.
  - 3) Cytotoxic agents: Cisplatin-based chemotherapy is often used for patients with recurrent adrenal carcinoma in combination with mitotane.
- c. Prognosis
  - 1) Children have superior prognosis to adults.
  - 2) Stage is the most significant prognostic indicator.
    - a) Stage I
      - i) Tumor 5 cm or smaller, no local invasion, negative nodes
      - ii) Five-year survival is up to 33% to 66%.
    - b) Stage II
      - i) Tumor greater than 5 cm, no local invasion, negative nodes.
      - ii) Five-year survival is up to 20% to 58%.
    - c) Stage III
      - i) Local invasion into periadrenal fat or positive nodes without local invasion
      - ii) Five-year survival is 18% to 24%.
    - d) Stage IV
      - i) Metastatic disease or locally invasive tumor with positive nodes
      - ii) Five-year survival is less than 5%.
      - iii) More than 40% of patients present with stage IV disease.

2. **Neuroblastoma** is addressed in Chapter 28.
3. **Benign adenoma:** Benign tumor of the adrenal cortex
   - a. Prevalence of up to 6% in large autopsy series
   - b. Rich in intracellular lipid, resulting in characteristic imaging features

   c. No treatment necessary if diagnosis of nonfunctional adenoma can be established with certainty.
   d. Two percent of metabolically silent adenomas can gain function at follow-up.
4. **Oncocytoma:** Unlike renal lesions, high percentage of adrenal oncocytomas prove malignant.
5. **Myelolipoma:** Rare, benign, nonfunctional cortical tumor consisting of fat and hematopoietic elements.
   a. Diagnosis easily made on imaging. Macroscopic fat is present.
   b. No treatment is necessary.
   c. Metabolic workup is suggested because concurrent functional adenomas can occur.
6. **Cysts:** Rare adrenal lesions seen in approximately 0.2% of autopsies; associated with 6% chance of malignancy
7. Metastasis
   a. Most common primary is the lung followed by kidney.
   b. Fine-needle aspiration is helpful in differentiating primary adrenal mass from metastatic disease.

## Evaluation of Adrenal Pathology in Urologic Practice

Urologists routinely face patients who are referred with an adrenal mass incidentally discovered on imaging (incidentaloma).

### IMAGING OF ADRENAL MASSES

Imaging characteristics, size, and interval growth of tumor are used to assess risk of malignancy. Imaging characteristics also afford ability to differentiate between various benign pathologic entities.

1. Imaging characteristics
   a. Ultrasound is rarely used to evaluate adrenals because normal glands and small nodules are difficult to visualize, especially on the left.
   b. Cross-sectional imaging with CT or MRI affords anatomical detail and quantification of intracellular lipid content.
      1) Macroscopic fat pathopneumonic for myelolipoma.
      2) Microscopic fat diagnostic of adrenal adenoma:

        a) Less than 10 Hounsfield units (HU) on noncontrast CT or signal dropout on out-of-phase sequences of opposed-phase chemical-shift MRI:
            i) Nearly 100% specific for adenoma
            ii) Seventy percent of adenomas exhibit this finding (remainder of lesions are lipid-poor).
        b) If more than 10 HU on noncontrast CT or lack of signal dropout on MRI requires 15 minute CT triphasic washout study:
            i) If lesions exhibit more than 60% absolute percent washout or more than 40% relative percent washout, largely diagnostic of adenoma
            ii) Lack of washout consistent with pheochromocytoma, metastasis, and potentially adrenocortical carcinoma.
    c. $^{125}$I-metaiodobenzylguanidine (MIBG) isotope scanning is selectively used for pheochromocytoma imaging when the possibility of metastatic, extraadrenal, or recurrent disease must be evaluated, but it is being replaced by FDG-PET.
    d. FDG-PET is reported to be both sensitive and specific for malignancy in cohorts with high pre-test probability of cancer.

2. Size and growth
    a. Adrenal lesions less than 4 cm can be observed, whereas masses greater than 6 cm (other than myelolipoma) should be resected. Resection of masses 4 to 6 cm should be considered in young and noncomorbid.
    b. Interval growth

    The current recommendation is to resect all incidentalomas that grow greater than 1 cm on follow-up imaging.

        1) Up to 25% of benign adenomas will have greater than 1 cm increase in size.
        2) Resection of lesions for interval growth seldom uncovers malignancy, especially if growth is sluggish.
3. Reimaging of adrenal masses is recommended at 6, 12, and 24 months after diagnosis, unless malignancy is a concern and more frequent imaging is deemed prudent.

## BIOPSY OF ADRENAL MASSES

1. Risk of bleeding, hypertension, track seeding, and disruption of surgical planes

2. Biopsy is unable to differentiate adenoma from carcinoma.
3. Only indicated to assess for adrenal metastasis if another known malignancy result will change management of adrenal mass; pheochromocytoma must be biochemically ruled out prior to biopsy.

## ASSESSMENT OF FUNCTION OF ADRENAL MASSES

1. More than 10% of incidentalomas harbor metabolic function.
    a. 5.3% Cushing syndrome is subclinical in many patients.
    b. 5.1% pheochromocytoma
    c. 1% aldosteronoma
2. Metabolic workup: All adrenal masses greater than 1 cm in size must be assessed for metabolic function.
    a. Test for Cushing syndrome
        1) Low-dose dexamethasone suppression test: Most often utilized test for screening.
            a) Patient takes 1 mg of dexamethasone at 11 PM. The cortisol level drawn early the next morning should be less than 5 mcg/dL.
            b) Oral contraceptives can yield false-positive results.
        2) Late night salivary cortisol testing is an alternative to low-dose dexamethasone suppression test.
        3) Twenty-four-hour urinary cortisol now felt to not be adequately sensitive for initial screening purposes. Results are only meaningful in patients with normal renal function.
    b. Testing for pheochromocytoma
        1) Plasma-free metanephrines (greater than 4 x normal) or 24-hour urinary-fractionated metanephrines are the best initial screening studies to rule out pheochromocytoma 24-hour urinary metanephrines.
            a) Plasma-free metanephrines not as specific (i.e., more false positives); however, testing is streamlined because can be tested on same blood draw as cortisol, aldosterone, and renin levels.
            b) Alpha-blockers, tricyclic antidepressants, caffeine (within 24 hours), and acetaminophen (within 5 days) interfere with results.

- c. Testing for Conn syndrome
  - 1) Testing indicated only in patients with hypertension.
  - 2) Ratio of morning plasma aldosterone to plasma renin (greater than 30) and morning aldosterone level (greater than 15 ng/mL) are obtained as a screening test.
  - 3) Hypokalemia should be repleted because a low potassium level may lead to false-positive results.
  - 4) Potassium-sparing diuretics and mineralocorticoid blockers must be stopped for at least 6 weeks prior to testing.
  - 5) Most antihypertensive agents can be continued for initial testing.
    - a) Beta-blockers can lead to false-positive results and need to be stopped for confirmatory testing.
    - b) ACE-inhibitors: A minority of patients can exhibit false-negative results.
    - c) Calcium channel blockers do not affect testing.
  - 6) Adrenal vein sampling is mandatory prior to adrenalectomy because a large proportion of patients with hyperaldosteronemia and adrenal mass exhibit bilateral aldosterone hyperextretion and thus are not helped by adrenalectomy.
- d. Testing for adrenal sex steroids
  - 1) Routine screening of incidentalomas for androgen/estrogen secretion is not recommended unless adrenocortical carcinoma is highly suspected.
  - 2) Levels of 17-ketosteroid can be elevated in 24-hour urine samples of patients with virilizing adrenocortical carcinoma.
- e. **Repeat functional testing** annually for 3 to 4 years is recommended; however, only approximately 2% of initially metabolically silent adrenal masses gain function on follow-up.

## SUMMARY OF SURGICAL INDICATIONS (FIGURE 22-2)

1. Functional adrenal mass
2. Increased risk of malignancy
   - a. Worrisome radiographic findings

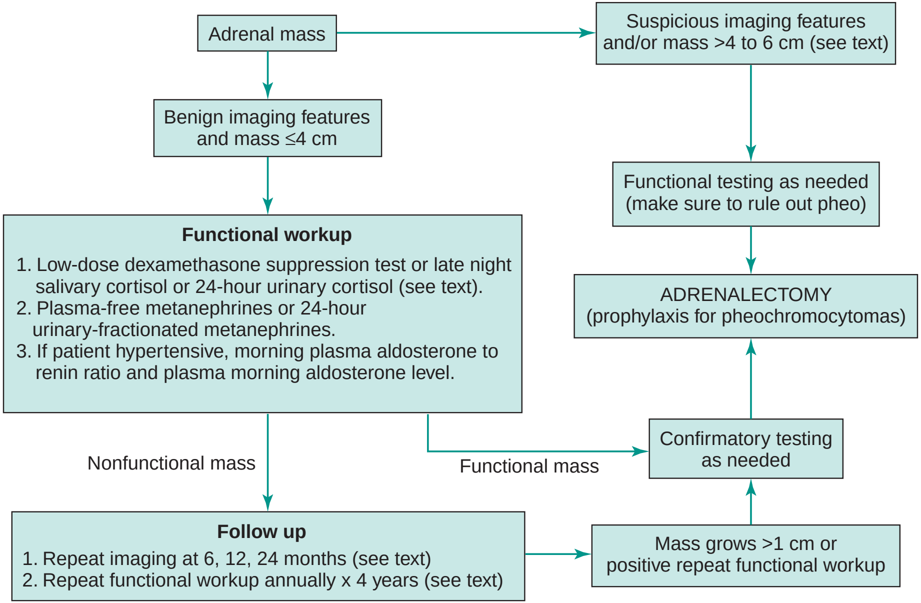
Adrenal mass
Suspicious imaging features and/or mass >4 to 6 cm (see text)
Benign imaging features and mass ≤4 cm
Functional testing as needed (make sure to rule out pheo)
Functional workup
1. Low-dose dexamethasone suppression test or late night salivary cortisol or 24-hour urinary cortisol (see text).
2. Plasma-free metanephrines or 24-hour urinary-fractionated metanephrines.
3. If patient hypertensive, morning plasma aldosterone to renin ratio and plasma morning aldosterone level.
ADRENALECTOMY (prophylaxis for pheochromocytomas)
Nonfunctional mass
Functional mass
Confirmatory testing as needed
Follow up
1. Repeat imaging at 6, 12, 24 months (see text)
2. Repeat functional workup annually x 4 years (see text)
Mass grows >1 cm or positive repeat functional workup

**FIGURE 22-2 Management algorithm for newly diagnosed incidental adrenal mass.** (Modified from Kavoussi LR, Schwartz MJ, Gill IS. Laparoscopic surgery of the kidney. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders, pp. 1628-1669.)

## DIFFERENTIAL DIAGNOSIS OF ADRENAL MASS

| Adrenal Pathologic Subtype | Malignant Potential | Incidence | Metabolic Activity | Radiographic Characteristics | Recommended Treatment |
|---|---|---|---|---|---|
| Adrenocortical carcinoma | Malignant | 0.5 to 2 per million/~300 cases in US per year | Up to 50% nonfunctional<br>Hypercortisolism most common<br>Virilization 10%-20%<br>Feminization 6%-10%<br>Hyperaldosteronism <5% | Mean nonenhanced CT attenuation 39 HU, ~100% >10HU<br>No signal dropout on in and out of phase MRI<br>Generally lack of contrast washout at 15 min on CT (exceptions exist in literature) | Resection<br>Mitotane<br>Cytotoxic chemotherapy |
| Adenoma | Benign | 6% of population on autopsy | 6% hypercortisolism<br>1% hyperaldosteronism | Mean nonenhanced CT attenuation 8HU,<br>70% <10HU<br>70% signal dropout on in and out of phase MRI<br>>95% contrast washout at 15 min on CT | Resection if metabolically active or if large (>4 cm in young noncomorbid, >6 cm in elderly comorbid); cannot be differentiated from ACC on percutaneous biopsy |
| Myelolipoma | Benign | ~0.1% of population | None, but metabolic work-up indicated because can mask small functional adenomas | Macroscopic lipid content on CT/MRI | No treatment necessary |

| Adrenal Pathologic Subtype | Malignant Potential | Incidence | Metabolic Activity | Radiographic Characteristics | Recommended Treatment |
|---|---|---|---|---|---|
| Pheochromocytoma | 5% malignant (high rates of malignancy in extraadrenal disease)<br>95% benign | 1-2 per 100,000 | Excess catecholamine secretion best tested via interrogation of metanephrine (metabolic byproducts) levels | >10HU on noncontrast CT (cases of lipid-rich pheos reported)<br>No signal dropout on in and out of phase MRI<br>Generally lack of contrast washout at 15 min on CT | Resection with appropriate perioperative catecholamine blockade/monitoring |
| Ganglioneuroma | Benign but can encase critical structures (e.g., great vessels) | Exceedingly rare | None, but metabolic workup necessary because definitive diagnosis cannot be made preoperatively | Generally <40HU on noncontrast CT with stippled calcifications | Diagnosis made upon resection |
| Cysts | Benign but up to 7% associated with malignancy | ~0.1% of population on autopsy | None, but generally metabolic workup advised | Well-circumscribed nonenhancing cystic lesions often with associated calcifications | Generally, resection in young and noncomorbid patients |

*(Continued)*

### DIFFERENTIAL DIAGNOSIS OF ADRENAL MASS—cont'd

| Adrenal Pathologic Subtype | Malignant Potential | Incidence | Metabolic Activity | Radiographic Characteristics | Recommended Treatment |
|---|---|---|---|---|---|
| Oncocytoma | 30% malignant<br>70% benign | ~50 case reports in literature | 10% secrete sex steroids, cytokines, and/or cortisol | No characteristic radiographic signature | Diagnosis made upon resection |
| Metastases | Malignant | 51% of all mets to adrenal stem from lung<br>28% from kidney | None | >10HU on noncontrast CT<br>No signal dropout on in and out of phase MRI<br>Generally lack of contrast washout at 15 min on CT | Adrenal metastasectomy utilized in patients with solitary adrenal metastases from lung and kidney |

b. Nonfunctional mass greater than 4 cm in young and/or noncomorbid and greater than 6 cm in patients for whom adrenalectomy risks are nontrivial.
c. Nonfunctional mass that is rapidly increasing in size.

## CLINICAL PEARLS

1. All adrenal masses require a metabolic work-up.
2. Adrenal CT washout study is superior to MRI in characterizing indeterminate adrenal masses.
3. Adrenal biopsy cannot differentiate between adrenal adenoma and adrenal carcinoma.
4. Possibility of pheochromocytoma must be ruled out before biopsy or surgery.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

*A 43-year-old man presents to your office following an emergency room visit for left renal colic. Noncontrast CT obtained in the emergency room revealed a 3-mm left distal ureteral stone and a 3.4-cm right adrenal mass measuring 5 HU in attenuation. By the time of the office visit, the patient is pain free and the stone has passed.*

1. *What is your management?*
2. *What is your management if the adrenal mass measured 15 HU?*

*A 25-year-old woman with hypertension, severe headaches, and weight loss is referred to your practice by her family-practice physician following diagnosis of pheochromocytoma in the left adrenal gland.*

3. *How do you prepare this patient for surgery?*
4. *Intraoperatively, the patient's blood pressure is steadily climbing as you perform the retroperitoneal dissection. As the certified registered nurse anesthetist (CRNA) pages the attending anesthesiologist, which medication do you instruct him to start?*
5. *At the postoperative visit, you inform the patient that the pathology report indicates that the lesion is benign. The patient asks you about her chances of recurrence and if any further follow-up is necessary. How do you counsel this patient?*

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## CHAPTER 23

# Retroperitoneal Tumors and Retroperitoneal Fibrosis

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## Retroperitoneal Anatomy

Retroperitoneal anatomy is a topic in which all practicing urologists should be well versed. Multiple disease entities, both urologic in origin and otherwise, occur in the retroperitoneum and are treated by urologists. The retroperitoneal space is bounded anteriorly by the posterior parietal peritoneum, superiorly by the diaphragmatic reflection, inferiorly by the pelvic diaphragm, and posteriorly by the muscles of the body wall.

Anatomic structures from virtually every organ system lie within or traverse the retroperitoneum. This includes major vascular structures such as the aorta and inferior vena cava (IVC) and many of their critical branches. Large nerve plexuses associated with the great vessels, including the celiac, hypogastric, and sacral plexuses, can all be found in the retroperitoneum. Portions of the gastrointestinal tract, including the pancreas and portions of the duodenum and colon, lie within the retroperitoneum. Finally, multiple structures specific to the practice of urology are found in the retroperitoneum, including the kidneys, adrenal glands, and ureters.

## Benign Diseases of the Retroperitoneum

### RETROPERITONEAL FIBROSIS

Idiopathic retroperitoneal fibrosis is an uncommon entity that generally affects adults between 40 and 60 years of age. Men have a two to three times higher incidence than women. Children and adolescents are rarely afflicted. Classically, idiopathic retroperitoneal fibrosis appears as a dense mass in the center of the retroperitoneum, usually at the L4 to L5 vertebral level. It can envelope the great vessels and extend from the aortic bifurcation superiorly to the renal pedicles and laterally beyond the psoas muscle. The inflammatory process can involve almost any retroperitoneal structure, and involvement outside of the retroperitoneum has occasionally been observed.

There are many well-documented causes of retroperitoneal fibrosis (Table 23-1) and a thorough evaluation must be completed before the diagnosis of idiopathic retroperitoneal fibrosis can be made. **It is paramount to exclude a primary or metastatic malignancy as the cause of retroperitoneal fibrosis.**

Retroperitoneal fibrosis can present with a variety of clinical signs and symptoms, depending on the degree of fibrosis and the organs affected. Symptoms generally begin insidiously, often starting out as vague complaints. Patients can present with abdominal and flank pain, malaise, anorexia, weight loss, nausea, or vomiting. Patients may initially present in renal failure secondary to ureteral obstruction. With such a variety of symptoms and presentations, a high index of suspicion is needed to not overlook the diagnosis of retroperitoneal fibrosis.

TABLE 23-1 **Causes of Retroperitoneal Fibrosis**

| | | |
|---|---|---|
| Drugs | Malignancies | Infections |
| Methysergide | Primary retroperitoneal tumors | Chronic UTI |
| Beta-blockers | Metastatic retroperitoneal tumors | Tuberculosis |
| Ergot alkaloids | Carcinoid retroperitoneal tumors | Gonorrhea |
| Haloperidol | Chemicals | Syphilis |
| Reserpine | Asbestos | Inflammatory processes |
| Phenacetin | Talcum powder | Endometriosis |
| Methyldopa | Avitene | Sarcoidosis |
| LSD | Iatrogenic | Collagen vascular disease |
| Amphetamines | Radiation | |
| Traumatic | | |
| Hemorrhage | | |
| Urinary extravasation | | |
| Postsurgical | | |

*LSD*, Lysergic acid diethylamide; *UTI,* urinary tract infection.

Multiple imaging modalities are useful in the diagnosis of retroperitoneal fibrosis. Classically, the triad of proximal hydroureteronephrosis, medial ureteral deviation, and extrinsic compression of the ureters was noted on intravenous pyelography; however, this imaging modality is used less frequently now. Patients presenting with an elevated creatinine level are often initially evaluated with ultrasonography or with a noncontrast computed tomography (CT) scan. **Noncontrast CT of the abdomen and pelvis allows for visualization of the extent of fibrosis; however, in patients with normal creatinine levels, CT scanning with intravenous contrast permits further evaluation of lymphadenopathy, fibrosis, and possible malignancy.** Laboratory tests are nonspecific for the diagnosis of retroperitoneal fibrosis. As in many inflammatory conditions, erythrocyte sedimentation rates and gamma globulin levels are often elevated.

In patients presenting with acute renal failure and bilateral obstruction, decompression of the urinary tract and restoration of metabolic homeostasis are a must prior to definitive treatment of the retroperitoneal fibrosis. This can usually be done with ureteral stenting, but in cases in which stent placement fails or it is unsafe to give a general anesthetic, percutaneous nephrostomy tubes should be placed. Once an acute obstruction has been relieved or in the patient presenting without acute renal failure, care must be taken to rule out a primary or metastatic malignancy as the cause of retroperitoneal fibrosis prior to instituting definitive therapy. **Should any ambiguity of diagnosis remain following a complete workup, a biopsy should be performed to definitively rule out malignancy.** This may be carried out via an open, laparoscopic, or percutaneous route depending on the disease location and the patient's abdominal anatomy.

First-line treatment for idiopathic retroperitoneal fibrosis can be either medical or surgical, depending both on physician and patient preference. Medical therapies for retroperitoneal fibrosis include glucocorticoids and immunosuppressive therapies. Glucocorticoids have been used with variable success in the literature. No standardized dosing schedule exists, but treatment should not be abandoned early because regression of the fibrotic plaque can be seen up to 20 months after steroid therapy.

Typically, patients are treated with 1 to 2 months of high-dose steroids and then slowly tapered down over the remaining treatment time. Immunosuppressant therapy has been reported both in combination with glucocorticoid treatment and as a single-line therapy. There are published reports of success with azathioprine, cyclophosphamide, penicillamine, and mycophenolate mofetil.

Should medical therapies fail or not be the desire of the patient, surgical exploration with ureterolysis can be performed. Preoperative ureteral stent placement greatly aids in ureteral dissection. At the time of surgical exploration, deep biopsies should be performed to rule out any undiagnosed malignancy. Once the ureters are completely freed of the fibrotic plaque, they can be intraperitonealized or wrapped with omentum to ensure surgical success. **Regardless of whether the disease process is unilateral or bilateral, a bilateral ureterolysis should be performed.** Postoperative steroid therapy is often used in an attempt to prevent recurrence.

## RETROPERITONEAL HEMORRHAGE

Spontaneous retroperitoneal hemorrhage is a rare event and can occur in a wide variety of age groups depending on etiology. The causes of retroperitoneal hemorrhage are numerous (Table 23-2). When the bleeding is renal in origin, it has been classically referred

TABLE 23-2 **Causes of Spontaneous Retroperitoneal Hemorrhage**

| **Retroperitoneal Tumors** | |
|---|---|
| Benign | Malignant |
| Angiomyolipoma | Renal cell carcinoma |
| Lipoma | Sarcoma |
| Adenoma | Wilms tumor |
| Fibroma | Granulosa cell tumors |
| Hamartoma | |
| Papilloma | |
| Hemorrhagic renal cyst | |
| Vascular | Hematologic |
| Panarteritis nodosa | Anticoagulation therapy |
| Renal artery arteriosclerosis | Hemophilia |
| Renal artery aneurysm rupture | Blood dyscrasia |
| Aortic aneurysm rupture | |

to as Wunderlich syndrome. After further workup, this is frequently found to be the initial presentation of a renal angiomyolipoma, which is, in fact, the most common cause of spontaneous retroperitoneal hemorrhage. Patients may present with a variety of symptoms, including back, flank, abdominal, hip, or upper thigh pain. Physical examination may be significant for flank ecchymosis, hypotension, hypovolemic shock, or gross hematuria. Cross-sectional radiographic imaging (usually CT) is most useful in documenting the possible cause and extent of the bleed.

Patients should be resuscitated with intravenous fluids and/or blood transfusions as needed. Any anticoagulant medications should be discontinued in the acute setting and any specific coagulopathies treated and reversed. Patients can be monitored with serial imaging to evaluate for resolution of the hematoma and bleeding. In cases in which conservative therapy fails to stabilize the patient, angiography with selective embolization of active bleeding vessels can be performed. **Retroperitoneal exploration should be approached with caution because it often results in massive blood loss and, when bleeding is renal in origin, nephrectomy.** Repeat imaging should be obtained after complete resolution of the hematoma to rule out malignancy as a cause of the spontaneous bleeding.

## PELVIC LIPOMATOSIS

Pelvic lipomatosis is a benign condition in which an excessive deposition of mature unencapsulated fat is in the pelvic retroperitoneum. The etiology of pelvic lipomatosis is unknown. It is most common in the 20- to 50-year age range and occurs predominantly in men, with African American men having the highest incidence. Obesity is described as a common association.

Fifty percent of patients with pelvic lipomatosis will present with voiding dysfunction, including urinary frequency, dysuria, nocturia, and suprapubic tenderness. Constipation may also be a presenting feature. Physical exam is nonspecific, but a suprapubic mass may be palpated. Hypertension is present in a significant proportion of these patients as well as azotemia due to extrinsic compression of the ureters. Cystitis glandularis, cystitis cystica, and cystitis follicularis have been observed in association with pelvic lipomatosis in as high as 75% of patients in some series. This situation should merit special attention from urologists because cystitis glandularis is a potential premalignant lesion of bladder adenocarcinoma. **Pelvic lipomatosis has a classic "pear-shaped" or "teardrop-shaped" bladder on intravenous urogram**. The upper tracts can range from normal to severely dilated, and the distal ureters are typically deviated medially. CT scan can be useful in the diagnosis of pelvic lipomatosis, given its ability to identify fat.

Conservative management of pelvic lipomatosis includes weight reduction and routine radiographic evaluation to monitor for upper tract deterioration. In patients who develop worsening hydronephrosis or progressive azotemia, urinary tract decompression should be performed. Ureteral stenting, nephrostomy tube placement, ureteral reimplantation into the bladder dome, and urinary diversion have all been employed in this setting. Debulking of pelvic fatty tissue has also been reported with success but is technically difficult and not without potential significant complications, including large blood loss and bowel and urinary tract injury.

## MYELOLIPOMA

Myelolipomas are tumorlike growths of mature fat and bone marrow elements. They most commonly occur in the adrenal gland but may be seen in other extramedullary locations throughout the retroperitoneal and thoracoabdominal organs. These lesions are generally seen in patients older than 40 years and are typically smaller than 5 cm. Myelolipomas are typically found as incidental lesions during abdominal imaging. **They may be surgically removed if the patient is symptomatic; however, good evidence supports observation, even in large lesions.**

## LEIOMYOMA

Leiomyomas are benign tumors of smooth-muscle origin. They are most commonly found in the female reproductive organs, but they may also develop in the retroperitoneum and the urinary bladder. When found in the retroperitoneum, they can grow to be quite large. Leiomyomas are difficult to distinguish from malignant lesions based on imaging alone and are generally surgically excised for this reason. Leiomyomas can be distinguished from malignant leiomyosarcoma histologically because of their positivity for desmin.

**CLINICAL PEARLS**

***Benign Disease of the Retroperitoneum***

1. Once malignancy has been ruled out, the treatment of retroperitoneal fibrosis typically revolves around relief of ureteral obstruction through ureteral stenting, percutaneous nephrostomy tube placement, or ureterolysis.
2. Retroperitoneal hemorrhage is most commonly renal in origin. No matter the site, this can represent life-threatening bleeding and requires astute attention to resuscitation and source control.
3. Leiomyomas often grow very large in size and are difficult to distinguish radiographically from malignant lesions. They are generally surgically excised for this reason.

# Malignant Lesions of the Retroperitoneum

## INCIDENCE AND ETIOLOGY

Primary retroperitoneal sarcomas are rare tumors accounting for 0.1% to 0.2% of all malignancies and 10% to 20% of all soft tissue sarcomas. The incidence is approximately 2.7 cases per $10^6$ persons per year. One third of all malignant tumors arising in the retroperitoneum are sarcomas, with the rest representing organ-specific malignancies. They are most common in the sixth decade of life but can affect almost any age group. A fairly even distribution exists between both sexes, and there is no documented racial or ethnic predilection.

Information with regard to risk factors for retroperitoneal sarcomas is sparse, but prior radiation, trauma, and environmental exposure to dioxin and asbestos have all been documented. Approximately 0.1% of patients who have received radiation therapy will develop a sarcoma at or near the treatment site. **Malignant fibrous histiocytoma is the most common radiation-induced retroperitoneal sarcoma.**

Sarcomas are thought to develop from mesenchymal stem cells residing in muscle, fat, and connective tissues. Retroperitoneal sarcomas arise primarily from soft tissues of fibrous and adipose origin. Histologically, liposarcoma is the most common form, followed by leiomyosarcoma and fibrosarcoma. Specific chromosomal transformations have been found for many of these tumors resulting in the production of tumor-specific transcription factors. Abnormalities on chromosome 12 resulting in amplification of certain gene products involved in p53 inactivation have also been cited in the carcinogenesis of retroperitoneal sarcomas.

## PATHOLOGY

Liposarcomas are the most common primary retroperitoneal tumor, comprising 10% to 15% of all soft tissue sarcomas, with approximately 20% of all liposarcomas being retroperitoneal in origin. They are most commonly seen during the fifth to sixth decade of life and can grow to be quite large in size. Grossly, liposarcomas have a “fish flesh” appearance and tend to be encapsulated. Well-differentiated liposarcomas can closely resemble lipomas and are classified as low grade. Higher grade liposarcomas tend to bear little resemblance histologically to fat-filled structures. Even though higher grade lesions still tend to be encapsulated, they tend to be locally invasive and recur after local excision. Nearly 90% of poorly differentiated tumors metastasize.

Leiomyosarcomas are less common, accounting for less than 10% of all soft tissue sarcomas. Up to 50% of these tumors occur in the retroperitoneum. They occur more frequently in women, with a 2:1 female-to-male incidence, and are found most commonly in the sixth decade of life. Low-grade lesions can be distinguished from leiomyomas by the increased number of mitoses seen with high-power microscopy (more than five mitoses per high-power field). **There is no definitive evidence that these sarcomas arise from malignant degeneration of leiomyomas.** A rare variant of retroperitoneal leiomyosarcomas originates from the great vessels.

Malignant fibrous histiocytoma (MFH) was first described in 1963 and is now the most common contemporarily reported soft tissue sarcoma. The seemingly increasing incidence is owing to the fact that many pleomorphic variants of fibrosarcoma, liposarcoma, and rhabdomyosarcoma have been reclassified into this category. These lesions are most frequently seen on the extremities, less commonly occurring in the retroperitoneum. There are several subtypes of MFH, including storiform-pleomorphic, myxoid, giant cell, and inflammatory. Several histologic subtypes can occur in the same lesion. The storiform-pleomorphic pattern is most common (40% to 60% of all MFH) and is histologically identified by its collagen pattern of curling fascicles of cells.

Despite the increasing incidence of MFH, rhabdomyosarcoma is still a commonly diagnosed lesion in pediatric urologic oncology patients. However, it is rarely seen in the adult population as a primary retroperitoneal tumor. Several subtypes exist, including embryonal, botryoid, alveolar, and spindle cell, with embryonal being the most common.

## DIAGNOSIS

**Because of their relatively slow growth and concealed location, retroperitoneal sarcomas are generally quite large at the time of diagnosis.** Symptoms are generally due to tumor mass effect or local invasion. The vast majority of patients will present with abdominal pain or an abdominal mass (60% to 80%). Twenty percent to 30% will have accompanying nausea, vomiting, early satiety, and weight loss. Urinary symptoms tend to be infrequent. On physical exam, a protuberant abdomen is often easily identifiable. Palpable lymphadenopathy is uncommon, found in approximately 5% of presenting patients. Lower extremity edema can be seen in approximately 20% of patients, usually because of extrinsic compression of the IVC. If a tumor arises primarily from retroperitoneal vessels, presentation correlates with the vessel involved (e.g., lower extremity edema for iliacs, Budd-Chiari syndromic findings if suprahepatic or intrahepatic IVC).

Cross-sectional imaging with either CT or magnetic resonance imaging (MRI) is essential in the workup of patients suspected of having a retroperitoneal mass. The size of the mass, its relationship to other important anatomic structures, the presence of lymphadenopathy, and visceral metastases can all be assessed with these modalities. CT is also excellent for the detection of bony invasion. If there is a question of vascular involvement after initial imaging, it is often advisable to obtain magnetic resonance angiography to more precisely delineate the relationship of important vascular structures to the retroperitoneal mass.

**If imaging does not provide a diagnosis with reasonable certainty, CT or ultrasound-guided biopsy may be used to obtain a tissue diagnosis.** Because of the infrequency of these lesions and the low sensitivity and specificity of diagnostic biopsy of these lesions in inexperienced hands, it is recommended that biopsies be performed at a center experienced in dealing with masses of this nature. In specific cases, open biopsy can be performed. Independent of the operative approach, care must be taken during biopsy to avoid tumor spillage.

## STAGING

Tumor grade plays an integral role in the staging of primary retroperitoneal tumors. Tumor grading is determined by the number of atypical mitoses, cytoplasmic and nuclear pleomorphism, and the presence of necrosis. Tumors are graded from well differentiated (low grade) to poorly differentiated (high grade) in a three-tier system (G1 to G3). The TNM system is combined with tumor grading (GTNM system) for the complete clinical staging of these tumors (see Table 23-3 and Table 23-4).

TABLE 23-3 **American Joint Commission on Cancer (AJCC) Grade-Tumor-Node-Metastasis (GTNM) Classification of Soft Tissue Sarcomas (2010)**

| | |
|---|---|
| ***Tumor Grade*** | |
| G1 | Well differentiated |
| G2 | Intermediately differentiated |
| G3 | Poorly differentiated |
| ***Primary Tumor*** | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 5 cm or less in greatest dimension* |
| T1a | Superficial tumor |
| T1b | Deep tumor |
| T2 | Tumor more than 5 cm in greatest dimension |
| T2a | Superficial tumor |
| T2b | Deep tumor |
| ***Regional Lymph Node Involvement*** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1** | Regional lymph node metastasis |
| ***Distant Metastasis*** | |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

* Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

** *Note*: Presence of positive nodes (N1) in M0 tumors is considered Stage III.

*(From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC Cancer Staging Manual, ed 7, New York, 2010, Springer.)*

TABLE 23-4 **AJCC Staging of Soft Tissue Sarcomas** (2010)

| | | | |
|---|---|---|---|
| IA | | | |
| T1a | N0 | M0 | G1, GX |
| T1b | N0 | M0 | G1, GX |
| IB | | | |
| T2a | N0 | M0 | G1, GX |
| T2b | N0 | M0 | G1, GX |
| IIA | | | |
| T1a | N0 | M0 | G2, G3 |
| T1b | N0 | M0 | G2, G3 |
| IIB | | | |
| T2a | N0 | M0 | G2 |
| T2b | N0 | M0 | G2 |
| III | | | |
| T2a, T2b | N0 | M0 | G3 |
| Any T | N1 | M0 | Any G |
| IV | | | |
| Any T | Any N | M1 | Any G |

*(From Edge SB, Byrd DR, Compton CC, et al, editors:* AJCC Cancer Staging Manual*, ed 7, New York, 2010, Springer.)*

Clinical staging should include a thorough physical examination, bone scan, and CT of the chest, abdomen, and pelvis. It is beneficial to obtain information on bilateral renal function prior to exploration in case nephrectomy is warranted intraoperatively.

## SURGERY

Extirpative surgery is the most effective form of therapy for patients with primary retroperitoneal tumors. **Complete resection, with negative margins, has proven to be the most important predictor of favorable outcomes in this patient population.** It is essential to be aware of the extent of the disease preoperatively and the organs that potentially may need to be sacrificed to optimize the chances of obtaining a negative margin.

The surgical approach is generally through a large midline, chevron, or thoracoabdominal incision. Regardless of approach, it is of paramount importance to gain wide exposure to the retroperitoneum to assess resectability and safely resect tumor. En bloc removal of all tumor and affected organs is essential for good patient outcomes, and it is very common to require removal of at least one adjacent organ in order to obtain negative margins.

Major vascular structures, kidneys, portions of the diaphragm, liver, stomach, gallbladder, spleen, pancreas, and bowel can all be involved. **The most frequently resected organ is the ipsilateral kidney, followed by a portion of the colon, adrenal gland, pancreas, and spleen.**

Surgical morbidity and mortality in contemporary series range from 6% to 25% and 2% to 7%, respectively. Hemorrhage, intraabdominal abscess, and enterocutaneous fistula formation are commonly described complications.

## OUTCOMES

Classically, the overall survival for patients with primary retroperitoneal sarcomas has been poor. Two-, 5-, and 10-year survivals have been cited at 56%, 34%, and 18% for all outcomes. In patients without metastatic disease, 2- and 5-year survivals can be as high as 70% and 50% to 60%, respectively.

Patients receiving a complete surgical resection with negative margins achieve superior survival compared to patients in which complete surgical resection is incomplete. Five-year survival for patients with complete surgical resection averages 54% compared to 17% for those with incomplete resections. Unfortunately, tumor recurrence, even after complete surgical resection, is the rule rather than the exception. **Tumor recurrence can be as high as 70% at 5 years and up to 90% at 10 years.** In the absence of metastatic disease, surgery is the mainstay of treatment for recurrent local disease. Studies support that a significant number of patients can experience prolonged disease-free survival when all recurrent tumor can be resected.

Tumor grade has a significant impact on patient survival. Low-grade lesions demonstrate an approximately 50% survival advantage compared to intermediate and high-grade lesions. This survival advantage is maintained regardless of margin status.

Given that the vast majority of failures occur in the abdomen, with an additional 20% to 30% of recurrences in the lungs, a surveillance regimen including physical examination, combined with CT of the chest, abdomen, and pelvis, appears to be a reasonable approach. The current guidelines from the National Comprehensive Cancer Network for the surveillance of retroperitoneal sarcomas include physical examination with chest, abdomen, and pelvic CT at strict intervals. For low-grade disease, this is carried out every 3 to 6 months for 2 to 3 years then annually thereafter. For high-grade disease, the schedule is every 3 to 4 months for 3 years, then every 6 months for 2 years, and annually thereafter.

## RADIATION AND CHEMOTHERAPY FOR RETROPERITONEAL SARCOMA

Much of the data supporting the use of radiation therapy and chemotherapy for treatment of sarcoma comes from the extremity sarcoma literature; however, there is growing evidence with these applications for retroperitoneal diseases as well. The use and timing of radiotherapy in patients with retroperitoneal sarcoma is controversial.

Retrospective studies on the benefit of adjuvant radiotherapy have yielded mixed results, but a decrease in local recurrences has been cited in some studies. Postoperative radiation has been associated with significant gastrointestinal toxicities. Intraoperative radiotherapy has been used in a small amount of patients at specialized centers. Intraoperative radiotherapy allows for the ability to directly target the resection bed while sparing nearby radiosensitive tissue. Neoadjuvant radiation therapy has the benefit of requiring a lower dose. **Additionally, toxicity may be lower preoperatively because the mass effect of the tumor often displaces organs out of the treatment field and the lack of surgical adhesions decreases the risk of bowel toxicity.** However, most series have been difficult to interpret because of combined regimens with brachytherapy or intraoperative radiation therapy. Attempts at phase III trials have been limited by poor accrual.

The exact role and benefit of chemotherapy in the treatment of retroperitoneal sarcomas is also controversial. Modest benefits have been noted using adjuvant doxorubicin chemotherapy in patients with extremity sarcomas, but these benefits are difficult to extrapolate to patients with retroperitoneal sarcomas. **For patients with advanced or metastatic disease doxorubicin is the principal chemotherapeutic agent.** A response rate of 20% to 25% has been noted, but complete or sustained responses are rare. A 4% overall survival advantage has been seen in patients with high-grade lesions. Combination agents have been employed but have not demonstrated superior responses compared to single-agent treatment and have shown significantly increased rates of toxicity.

## CLINICAL PEARLS

***Malignant Lesions of the Retroperitoneum***

1. Due to their relatively slow growth and concealed location, retroperitoneal sarcomas are generally quite large at the time of diagnosis. Symptoms are generally due to tumor mass effect or local invasion.
2. Surgical resection is the most effective form of treatment for primary retroperitoneal tumors. Complete resection, with negative margins, is the most important predictor of outcome.
3. Radiation therapy may be administered pre-, intra-, or postoperatively. Chemotherapy has a limited role in the treatment of retroperitoneal sarcomas, but doxorubicin represents the most commonly used agent.

## DIFFERENTIAL DIAGNOSIS

**Retroperitoneal Fibrosis**

- Aortic aneurysm
- Carcinoid
- Infectious process (histoplasmosis, actinomycosis, tuberculosis)
- Inflammatory bowel disease
- Lymphoma
- Metastatic disease (colon, breast, lung, genitourinary, thyroid)
- Pancreatitis
- Retroperitoneal sarcoma
- Retroperitoneal hemorrhage

**Retroperitoneal Hemorrhage**

- Great vessel rupture
- Hematologic origin (anticoagulation therapy, blood dyscrasias)
- Iatrogenic (percutaneous or vascular procedure)
- Pancreatic hemorrhage
- Renal hemorrhage (angiomyolipoma)

**Retroperitoneal Tumor**

- Direct extension of local tumor (renal, adrenal)
- Hamartoma
- Lipoma
- Leiomyoma
- Metastatic disease (colon, breast, lung, genitourinary, thyroid)
- Sarcoma (liposarcoma, leiomyosarcoma)
- Schwannoma

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What are the potential treatments, both surgical and nonsurgical, for retroperitoneal fibrosis?*
2. *What are the possible etiologies of a spontaneous retroperitoneal hematoma?*
3. *What are the radiographic manifestations of pelvic lipomatosis, and what is the clinical significance of cystitis glandularis in the setting of pelvic lipomatosis?*
4. *What is the incidence of primary retroperitoneal sarcoma? What are the risk factors for development of this disease?*
5. *How does retroperitoneal sarcomas present clinically? How are they staged?*
6. *What is the most important predictor of outcome in patients with retroperitoneal sarcomas?*
7. *What is the role of radiation and chemotherapy in patients with retroperitoneal sarcomas?*

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## CHAPTER 24

# Renal Physiology and Pathophysiology

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## Introduction

An understanding of renal physiology helps provide a foundation for the practicing urologist to better understand the pharmacology, pathology, and therapies encountered in daily clinical practice. Urologists encounter issues pertaining to renal physiology and pathophysiology frequently, and this will only become more common as the prevalence of kidney disease nationwide increases with the aging population. It is the goal of this chapter to provide an overview of the basic concepts of renal physiology and pathophysiology for urologists.

## Acute Kidney Injury and Chronic Kidney Disease

### ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is defined as a rapid decline in GFR, often manifested by an increase in serum creatinine concentration. It is associated with increased morbidity, mortality, prolonged hospitalization, and healthcare costs. AKI can be divided into prerenal, intrarenal, and postrenal causes. The approach and treatment for these conditions differ and one or more of these conditions can coexist.

1. Prerenal AKI

   **Prerenal AKI results from underperfusion of the kidney, which stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone axis.** This results in renal vasoconstriction, increased ADH secretion, and increased sodium and water reabsorption in the tubules. Total urine volume decreases, urinary sodium concentration decreases, and urinary osmolarity increases. The urinalysis will appear bland.

Although hypotension is a common cause of prerenal AKI, it can still occur in the absence of major drops with systemic blood pressure. Disordered renal autoregulation can be seen in the elderly, those with renal artery stenosis, and in patients taking drugs that interfere with angiotensin II or prostaglandin synthesis, such as anigotensin-converting enzyme (ACE) inhibitors and nonsteroidal antiinflammatory drugs (NSAIDS).

2. Intrarenal AKI
   a. Acute interstitial nephritis (AIN)

AIN is a sterile inflammatory process that occurs within the renal parenchyma. Although many pathological processes can lead to AIN, the most common cause is a medication reaction. Many medications have been associated with AIN, but the highest risk is associated with the use of NSAIDS and antibiotics (particularly those containing beta-lactam moieties). AIN is an idiopathic reaction that is not dose dependent. AIN typically occurs within 3 to 5 days of exposure but may be delayed several weeks. It can occur in patients who have not previously had a reaction to the suspect medication. AIN typically presents with low-grade fever and worsening renal function. Urinalysis will usually show sterile pyuria and white blood cell (WBC) casts. Occasionally eosinophiluria can be seen with Hansel stain. About 25% will have a rash, and 75% will have eosinophilia and eosinophiluria. There is usually a modest degree of proteinuria secondary to the increased glomerular capillary permeability from cytokine release of infiltrating T cells. Only renal biopsy can confirm the diagnosis, but should be reserved for patients who do not improve within 3 to 7 days of drug discontinuation, or those with severe AKI. The use of corticosteroids to reduce interstitial fibrosis and speed renal function recovery is controversial.

   b. Acute glomerulonephritis

Glomerulonephritis results when a sterile inflammatory reaction is present within the glomerulus and can be triggered by a variety of disease states. Urinalysis is the key to diagnosis because both proteinuria and hematuria will be present.

Red blood cell (RBC) casts on microscopy is pathognomonic of glomerulonephritis. RBCs seen on microscopy will often appear dysmorphic, suggesting that they have traversed the glomerular basement membrane. Rapidly progressive glomerulonephritis is a clinical diagnosis characterized by the rapid loss of renal function, often over days to weeks, in the presence of glomerulonephritis and is a medical emergency.

c. Pigment nephropathy

Pigment nephropathy occurs when liberated heme pigments interact with the renal tubules leading to obstruction and necrosis. These pigments are released in the form of myoglobin in the setting of rhabdomyolysis or hemoglobin in cases of brisk hemolysis. Rhabdomyolysis can occur in the setting of trauma (particularly crush injury), certain infections, intoxications, or protracted surgical positioning. In the urology literature, it has been historically described after complex urethral stricture repair and prolonged laparoscopic renal surgery. Pigment nephropathy should be suspected when a urinary dipstick reveals blood (heme) but urinary microscopy is without RBCs. Patients with rhabdomyolysis should be aggressively fluid resuscitated to maintain a brisk urine output. Forced alkaline diuresis may minimize the nephrotoxicity of the toxic myoglobin that is released from damaged muscle cells, but this approach carries a risk of hypocalcemia and increased metastatic calcification.

d. Contrast induced nephropathy (CIN)

CIN occurs in roughly 1% to 2% of patients receiving iodinated contrast. The mechanism of renal injury is thought to be twofold; contrast is vasoconstrictive and may be directly cytotoxic. Patients with underlying kidney disease are at the highest risk. Patients with other comorbid conditions, including diabetes and CHF, are also at increased risk. **Greater awareness of CIN has led to a decreased incidence in the condition over the last several years. Preventive measures should be taken for at-risk patients, including low or iso-osmolar contrast agents, periprocedural IV hydration, and reduction in contrast volume. N-acetyl cysteine and sodium bicarbonate are frequently given as a preventive measure, but evidence for the effectiveness of this approach is lacking.**

e. Acute tubular necrosis (ATN)

**As the most common cause of acute renal failure in hospitalized patients, ATN affects up to 5% of inpatients and up to 30% of intensive care unit patients.** It usually results from persistent or extreme renal hypoperfusion resulting in ischemic injury to renal tubular cells or from agents that are directly cytotoxic to tubular cells. The list of potential nephrotoxic agents is long and includes antibiotics (aminoglycosides, sulfonamide, vancomycin), chemotherapeutics (cisplatin), and many others. Cellular debris is formed that obstructs tubular flow resulting in back-leakage of glomerular ultrafiltrate and vasculature congestion. The disrupted renal epithelium can no longer act as a barrier to free movement of solutes and water; therefore the kidney loses its ability to concentrate urine. Inflammatory mediators are also released that attract leukocytes. On urinalysis, patients with ATN will frequently have pigmented granular casts, sometimes called *muddy brown* casts.

Fortunately, the kidney has a remarkable capacity for recovery. Recovery from ATN typically occurs in three phases. The oliguric phase begins less than 24 hours after the inciting incident and can last 1 to 3 weeks; it may be more prolonged in the elderly. The oliguric phase is associated with metabolic disturbances, gastrointestinal bleeding, and infectious complications. Eventually daily urine volume progressively increases leading to the diuretic phase, which indicates the start of renal recovery. Serum creatinine may continue to rise for another 24 to 48 hours before it plateaus, then eventually falls. Nearly 25% of AKI-associated mortalities occur in the diuretic phase. Finally, in the recovery phase, renal function returns near baseline, but abnormalities of urinary concentration may persist for weeks.

3. Postrenal AKI

This usually occurs secondary to obstruction of the urinary tract which results in a backfilling of Bowman capsule disrupting glomerular filtration. The initial management of a patient with postrenal AKI should include assessing the patency of any device draining the urinary system (urinary catheters, nephrostomy tubes) that may be present. **Postrenal AKI should be suspected in all patients with a urological history, history of prior abdominal or pelvic surgery, malignancy, or radiation therapy.**

Postoperative fluid collections after retroperitoneal surgery can result in AKI from extrinsic compression. If urinary extravasation is suspected and a surgical drain is still in place, a drain creatinine to serum creatinine ratio can be checked. A ratio of more than 10:1 is diagnostic. If results are equivocal, then giving intravenous (IV) indigo carmine or methylene blue can be confirmatory. When postrenal AKI is suspected, a renal ultrasound should be obtained because it is about 90% to 95% sensitive and specific for hydronephrosis. False negatives may be seen in periureteral metastatic disease or retroperitoneal fibrosis. Obtaining renal radionuclide studies or retrograde pyelography is helpful to confirm the diagnosis of obstruction.

## APPROACH TO PATIENT WITH AKI

AKI should be interpreted in the light of the patient's baseline renal function (if known). All potential nephrotoxins should be immediately discontinued. **A timeline should be created with all interventions and potential nephrotoxic insults outlined against changes in renal function.** Volume status should be assessed and followed with daily weights and physical examination. Strict fluid input and output should be recorded with insensible losses factored in. Hypertension with advanced renal insufficiency suggests fluid overload, which may require diuretics or dialysis. Spun urine should be checked for sediment. In prerenal and postrenal settings, the sediment will appear bland, whereas pigmented casts will be seen in ATN, eosinophils in AIN, and RBC casts will be seen in acute glomerulonephritis. The fractional excretion of sodium (FENa) should also be calculated.

FENa = 100 × (urinary sodium concentration) × (plasma creatinine concentration) / (plasma sodium concentration) × (urinary creatinine concentration)

Initial management includes giving isotonic fluids to rule out prerenal causes and maintain normal volume status (provided the patient is not already volume overloaded). Medication dosages should be adjusted. Diuretic therapy has no benefit in oliguric patients. Nutritional support is very important in AKI to promote recovery of renal function because AKI is associated with a negative nitrogen balance. Phosphorous, potassium, and sodium intake may need to be limited. Oliguric patients may need to have their fluid intake limited.

TABLE 24-1 **Laboratory Values for AKI Workup**

| | UNa (mmol/L) | FENa |
|---|---|---|
| Prerenal | <20 | <1% |
| Intrinsic renal | >40 | >3% |
| Postrenal | >40 | >4% |

Hyperkalemia should be avoided, but if it develops, the first step should be to stabilize the cardiac membrane with IV calcium to prevent arrhythmia development. Potassium can be shifted intracellularly with insulin (always given after dextrose). Cationic-binding resins, such as sodium polystyrene (Kayexalate), can eliminate potassium from the body. Furosemide is useful to augment renal excretion of potassium if the patient is not anuric. If severe hyperkalemia develops, then dialysis may be required (see Table 24-1).

## INDICATIONS FOR DIALYSIS

Indications for dialysis include severe hyperkalemia, uremic symptoms, certain toxins, significant volume overload, and severe metabolic acidosis. **The determination for dialysis does not depend on a specific BUN or creatinine threshold.** Hemodialysis is the standard choice for stable patients with AKI, but it is important to realize that dialysis could potentially worsen ATN by inducing systemic hypotension and underperfusion to already damaged nephrons.

## CHRONIC KIDNEY DISEASE

Chronic kidney disease (**CKD**) **is defined as sustained kidney damage with GFR greater than 60 mL/min/1.73 $m^2$ for longer than 3 months.** Whereas small changes in serum creatinine correlate with significant GFR reduction when renal function is greater than 60 mL/min, in the setting of CKD, serum creatinine does not correlate well with changes in GFR. As GFR falls below approximately 20% of normal, progressive anorexia, salt retention, acidosis, anemia, and fatigue may occur.

Progression of CKD is thought to result from a reduction in total nephron mass after an insult (which may be acute or sustained) that causes renal damage. **Injury is associated with hyperfiltration, glomerular hypertrophy, and systemic hypertension. The reduced nephron mass predisposes the remaining nephrons to high glomerular pressures and further damage.** In response to injury, a complex interaction of multiple growth factors and cytokines results in structural changes and remodeling, which contributes to pathologic glomerulosclerosis and interstitial fibrosis.

**As GFR decreases, the rate of mortality and hospitalization increases. Similarly, as GFR decreases, the incidence of cardiovascular disease (CVD) increases, making CVD the leading cause of death in CKD patients.** Furthermore, the degree of albuminuria and the albumin-to-creatinine ratio (ACR) have also been correlated with outcomes for end-stage renal disease (ESRD). **A consensus statement issued from Kidney Disease: Improving Global Outcomes (KDIGO) suggests that renal impairment, GFR category, and albuminuria are the most useful prognostic factors for patients with CKD (Figure 24-2), (Table 24-2).**

## END-STAGE RENAL DISEASE

Most forms of CKD gradually progress to ESRD over 2 to 10 years depending on etiology and patient-specific factors. Diabetes accounts for almost 50% of patients with ESRD, followed by hypertensive nephropathy accounting for approximately 25%.

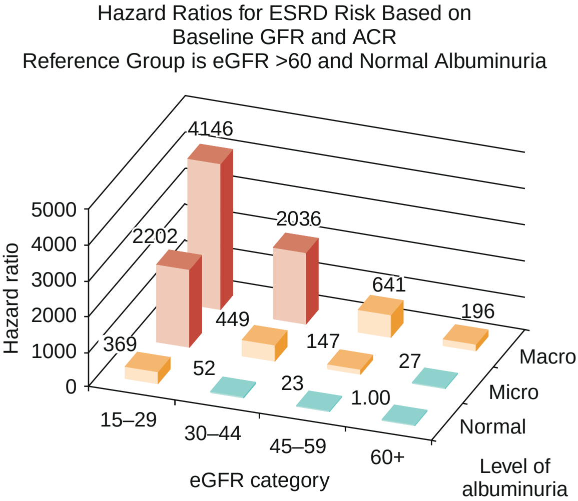

**FIGURE 24-2 Risk of end-stage renal disease (ESRD) correlates with albuminuria and glomerular filtration rate (GFR).** (Modified from Hallan SI, Ritz E, Lydersen S, et al: Combining GFR and albuminuria to classify CKD improves prediction of ESRD, *J Am Soc Nephrol* 20:1069–1077, 2009).

TABLE 24-2 **Stages of Chronic Kidney Disease (CKD)**

| CKD Stage | Glomerular Filtration Rate (GFR) | Description |
|---|---|---|
| 1 | ≥90 | Renal damage with hyperfiltration |
| 2 | 89–60 | Mild decrease in GFR |
| 3a | 59–45 | Mild to moderate decrease in GFR |
| 3b | 44–30 | Moderate to severe decrease in GFR |
| 4 | 29–15 | Severe decrease in GFR |
| 5 | <15 or dialysis | End-stage renal disease (ESRD) |

Hypertension is an even more common cause of ESRD in black Americans.

## CKD AND RENAL SURGERY

**Because of the risks associated with CKD and the subsequent development of CVD, an increasing importance has been placed on selecting nephron-sparing techniques for renal masses whenever feasible. Numerous retrospective studies have shown radical nephrectomy to be a risk factor for development of CKD, whereas partial nephrectomy may be able to minimize GFR reduction. It is estimated that over 25% of patients presenting with small renal masses already have a preoperative GFR less than 60 mL/min/1.73 $m^2$, highlighting the need to preserve every nephron possible.**

## RENOPROTECTIVE STRATEGIES FOR PATIENTS WITH CKD

Patients with an estimated GFR of less than 60 should have early referral to a nephrologist. The cornerstones to prevent progression of CKD are basic lifestyle modifications (e.g., diet, exercise), aggressive blood pressure control, glycemic control, and reduction in low-density lipoprotein cholesterol. Initiation of ACE inhibitor therapy should be considered to reduce the progression from microalbuminuria to overt nephropathy. Nephrotoxic agents should obviously be avoided.

## CLINICAL PEARLS

1. Several medications such as trimethoprim inhibit the secretion of creatinine into the tubule, which decreases creatinine clearance without changing the glomerular filtration rate (GFR).
2. Distal renal tubular acidosis is associated with recurrent calcium phosphate urolithiasis because the metabolic acidosis results in bone resorption with subsequent increased filtered load of calcium leading to nephrocalcinosis and stone formation. Proximal renal tubular acidosis is not associated with increased risk of nephrocalcinosis and stone formation despite increases in urinary calcium levels because urinary citrate levels are not reduced.
3. Declining renal function is associated with increased morbidity and mortality, particularly through increased cardiovascular disease (CVD). Radical nephrectomy is associated with iatrogenic renal insufficiency; therefore nephron-sparing surgery should be selected for treatment of renal masses whenever feasible.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

# Renal Physiology

## GLOMERULAR FILTRATION

The kidneys receive approximately 20% of the cardiac output resulting in renal blood flow of approximately one liter per minute. Blood flow to the kidney proceeds sequentially from the renal arteries to interlobar arteries, arcuate arteries, interlobular arteries, and then to the afferent arterioles. Afferent arterioles develop into the glomerular tuft, a capillary network which is the site of all renal filtration. The glomerular tufts evolve into the efferent arterioles which go on to form the vasa recta which provide oxygenated blood to the renal tubules. The kidney is the only place in the body in which a capillary bed connects two arterioles — a necessary development to ensure adequate filtration pressure in the glomerulus. **Renal blood flow is regulated by vascular resistance changes primarily of the efferent and afferent arterioles controlled by a complex interplay of neurohormonal signals in response to physiologic conditions.** A single arteriole–glomerulus–tubule system is referred to as a *nephron*.

Filtration of plasma across the glomerular membrane is the initial step in the formation of urine and the elimination of waste products from the blood. The fluid filtered through the glomerulus (and which will subsequently travel through the tubular system) is referred to as the *ultrafiltrate*. The glomerular filtration rate (GFR) is the sum of the GFRs of all individual nephrons and reflects overall renal function. GFR is determined by Starling forces.

GFR = Kf [(hydrostatic pressure in glomerulus – hydrostatic pressure in Bowman capsule) – (oncotic pressure in glomerulus – oncotic pressure in Bowman capsule)]

Kf is a coefficient accounting for glomerular membrane permeability and glomerular surface area. Because hydrostatic and oncotic pressure within Bowman space are relatively stable (and very low) under normal circumstances, GFR is determined primarily by the hydrostatic and oncotic pressure in the plasma. The permeability of the basement membrane is determined by characteristics of: (1) the fenestrated endothelial cells lining the glomerular capillary, (2) the glomerular basement membrane, and (3) the podocytes – epithelial cells surrounding the outside of the glomerular tuft.

**GFR is controlled by autoregulation, an incompletely understood process, which maintains renal blood flow across a wide**

**range of systemic blood pressures.** Autoregulation is mediated in part by myogenic mechanisms within the afferent arteriole. Feedback loops involving hormones and vasoactive substances also play a role. Autoregulation appears to be effective for the mean arterial pressure range of 40 to 70 mm Hg, but is less effective out of that range. Tubuloglomerular feedback also plays a significant role in regulating GFR. Tubuloglomerular feedback uses specialized cells within the macula densa of the distal tubule to sense the delivery of sodium and chloride and signal changes in efferent vascular resistance in response to changes in distal delivery.

## CALCULATING GLOMERULAR FILTRATION RATE

Measuring the actual GFR is not possible clinically, but GFR can be estimated by calculating the renal clearance of a substance that is freely filtered at the glomerulus and not secreted, reabsorbed, synthesized, or metabolized within the renal tubule.

Clearance = (urinary concentration of substance) × (volume of urine over time) / (serum concentration of substance)

Inulin or radiolabeled compounds can give the best estimate of GFR but are limited by the need for intravenous infusion at a constant rate and difficulty in measurement. Creatinine (Cr) clearance is the most commonly used surrogate for GFR in clinical settings. Creatinine is a breakdown product of muscle, which is produced at a fairly constant rate. Calculating the 24-hour creatinine clearance is a relatively simple way to estimate GFR. However, **approximately 10% to 20% of** creatinine **is secreted in the proximal tubule, which leads to an overestimate of true GFR. Notably, as true GFR declines, the amount of** creatinine **which is secreted increases and can contribute up to 35% of total** creatinine **excretion. At best,** creatinine **clearance represents the upper limit of the true GFR. It is also important for clinicians to be aware that several medications, such as trimethoprim, inhibit the secretion of** creatinine **into the tubule, which decreases** creatinine **clearance without changing GFR.** Creatinine levels also vary in settings of muscle loss or gain which also limits the accuracy of creatinine clearance.

Other markers of renal function are under investigation. The blood urea nitrogen (BUN) concentration is too variable by the patient's hydration and dietary protein intake to be clinically useful as a measure of GFR. Plasma cystatin C is a protein found in all nucleated cells that is produced at a constant rate and is unaffected by diet. Cystatin C is freely filtered, reabsorbed in the tubule system, and fully metabolized, preventing any reabsorption of cystatin C into the blood pool. Although cystatin C does have promise as a measure of GFR in the future, its use has been limited because serum levels are affected by acute disease processes, and cystatin C assays have limited availability.

Formulas to accurately predict GFR without collecting a timed urine sample have been developed and are of significant clinical importance. The Cockcroft-Gault formula is a simple mathematical correction that estimates creatinine clearance with improved accuracy over plasma Cr alone by correcting for age, sex, body mass, and weight. The Cockcroft-Gault formula was originally calculated using normal healthy individuals, and therefore it is less accurate in individuals with impaired renal function.

Cockcroft-Gault Formula for estimated GFR = (140 − age) × (body mass in Kg) × (0.85 of female) / (72) × (serum Cr in mg/dL).

Estimating GFR using the Modification of Diet in Renal Disease formula (MDRD) is more complex but more accurate than the Cockcroft-Gault formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was developed to improve the MDRD formula, particularly at higher GFR. Both MDRD and CKD-EPI give an estimated GFR from serum creatinine, age, gender, and race. Because of inaccuracies in estimation of GFR at the higher range, many clinical laboratories will report all GFRs that are above 60 mL/min/1.73 $m^2$ as *greater than 60*.

## TUBULAR PHYSIOLOGY

Once the ultrafiltrate leaves Bowman space, it travels along a tubular system in which the properties of the fluid are modified by secretion and reabsorption of various dissolved substances and water. These processes are mediated by osmotic gradients, electrochemical gradients, and active transport.

The proximal convoluted tubules (PCT) are the site of approximately 60% of reabsorption of the glomerular filtrate. About 65% of filtered sodium is reabsorbed by passive and active routes. About 90% of filtered bicarbonate is reabsorbed as well. Glucose is almost entirely reclaimed in the PCT; however, blood glucose levels above 200 mg/mL can exceed the transport threshold, resulting in glucosuria. The majority of filtered water, potassium, calcium, phosphate, and amino acids are also absorbed in the PCT.

The loop of Henle reabsorbs about 25% of sodium via a sodium-potassium-two-chloride cotransporter (NaK2Cl). This transporter is inhibited by “loop” diuretics, such as furosemide. The loop of Henle helps establish a medullary interstitial osmotic gradient — a concentration of solute within the medulla of the kidney that, at 1200 mOsm/L, is four times that of the serum. This hypertonic milieu is necessary to allow for the concentration of urine in the collecting duct. In addition, the thick ascending limb is where Tamm-Horsfall mucoprotein production and secretion occurs. Tamm-Horsfall proteins aid in the prevention of urinary tract infections and form the matrix for all urinary casts.

In the distal tubule, 5% to 10% of sodium is reabsorbed via the actions of an apical sodium-chloride cotransporter, which is inhibited by thiazide diuretics. About 10% to 15% of calcium is also absorbed via luminal channels. Calcium reabsorption is regulated mainly by parathyroid hormone (PTH), with higher levels of PTH increasing calcium reabsorption. Thiazide diuretics promote reabsorption of calcium and can be used as a medical treatment for calcium stone formers.

The collecting tubule contains two main cell types, principal cells and intercalated cells. Principal cells are responsible for sodium reabsorption and potassium secretion. In the presence of aldosterone, an apical sodium channel is opened allowing reabsorption of sodium, with an attendant efflux of potassium into the filtrate to maintain electrical neutrality. The epithelial sodium channel is inhibited by amiloride (a potassium-sparing diuretic). The collecting tubule is only permeable to water in the presence of antidiuretic hormone (ADH). When ADH is present, apical aquaporin channels are inserted into principal cells, allowing the efflux of water from the filtrate towards the hypertonic interstitium. ADH is released from the supraoptic nucleus of the hypothalamus in response to increased serum osmolality or hypovolemia.

Collecting tubule intercalated cells are responsible for acid handling. Type A intercalated cells actively secrete protons, whereas type B intercalated cells secrete bicarbonate into the filtrate. The relative magnitude of these processes will vary, depending on serum and cellular pH, and in general work to preserve a systemic pH of 7.4 (Figure 24-1).

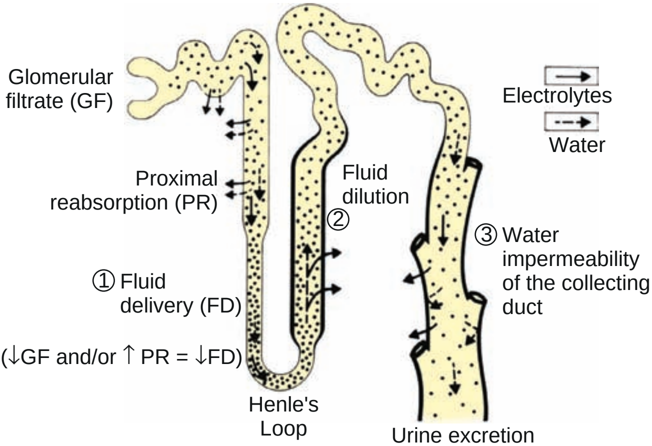

FIGURE 24-1 **Flow and dilution of urine in a single nephron.** (Redrawn from Berl T, Schrier RW: Water metabolism and the hypo-osmolar syndrome. In Brenner BM, Stein JH, editors. *Sodium and water homeostasis*. New York, 1978, Churchill Livingstone, pp. 1–23.)

## SODIUM AND WATER BALANCE

**Serum sodium concentration reflects both the total body sodium and total body water content. Perturbations in serum sodium concentration are nearly uniformly due to disturbances in water handling, rather than overconsumption or overexcretion of sodium.**

1. Hyponatremia

   Hyponatremia results when the rate of water intake exceeds the rate of water excretion. Most cases are due to failure of the kidneys to appropriately excrete excess water, often because of the (appropriate or inappropriate) presence of ADH. ADH is directly proportional to urine osmolarity, making urine osmolarity a critical test in the differential diagnosis of hyponatremia. ADH is appropriately elevated in states of true volume depletion (shock, trauma, bleeding) and volume overload states with relative intravascular volume depletion (congestive heart failure [CHF], cirrhosis, nephrotic syndrome). The ability of the kidney to excrete water can be overcome in the absence of ADH secretion by excessive water intake in the setting of psychogenic polydipsia. Symptoms of hyponatremia are proportional to the rate of decline in serum sodium concentration. **A severe or sudden rate of change in sodium concentration can lead to seizures, altered mental status, coma, or death.**

### DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA

| | **Low Uosm (Low ADH States)** | **High Uosm (High ADH States)** |
|---|---|---|
| Hypovolemic | | Diuretics, volume depletion (burns, blood loss, shock, trauma) |
| Hypervolemic | | Congestive heart failure (CHF), cirrhosis, nephrotic syndrome |
| Euvolemic | Psychogenic polydipsia, low solute intake (i.e., beer potomania, tea and toast hyponatremia) | Syndrome of inappropriate antidiuretic hormone secretion (SIADH), glucocorticoid deficiency, hypothyroidism, stress |

2. Hypernatremia

Hypernatremia is due to loss of water in the absence of adequate water intake. Because of the powerful effect of thirst on behavior, individuals with large water losses from urine and stool rarely become hypernatremic unless they are deprived access to water or have an impairment of thirst (as can be seen in dementia). The underlying cause of hypernatremia is best determined by volume status.

### DIFFERENTIAL DIAGNOSIS FOR HYPERNATREMIA

| | **Causes** |
|---|---|
| Hypovolemic | Failure of renal concentrating ability (furosemide, postobstructive diuresis) or extrarenal water loss (fistula, diarrhea, burns) |
| Hypervolemic | Metabolic (Cushing syndrome, hyperaldosteronism) or iatrogenic (excess intravenous sodium) |
| Euvolemic | Nephrogenic or central diabetes insipidus |

In general, management of hypernatremia focuses on water administration (either orally or, with 5% dextrose, intravenously). Patients with hypovolemia should be volume resuscitated with isotonic fluids simultaneously.

## POTASSIUM BALANCE

Serum potassium levels poorly reflect total body potassium because the majority of potassium is intracellular. After potassium loading (from dietary sources, for instance) potassium homeostasis is first achieved via shifts of potassium from the extracellular to intracellular space, and secondarily via urinary excretion, which is facilitated by aldosterone. Hyperkalemia (as manifested by elevated serum potassium concentration) manifests as muscle weakness and can lead to arrhythmia and death. Management of hyperkalemia requires augmenting the extracellular to intracellular shift of potassium (through the use of insulin, bicarbonate, and beta-adrenergic-agonists), and augmenting renal and gastrointestinal potassium excretion. Hypokalemia can also lead to weakness, ileus, and arrhythmia but is effectively treated with potassium supplementation.

## ACID-BASE BALANCE

Carbohydrate, protein, and fat metabolism results in the creation of acid byproducts. Several buffer systems exist to counteract the effect of acid loads and to allow time for renal mechanisms to excrete excess acid. Bicarbonate is the primary serum buffer, though proteins and phosphate also provide acid buffering. Carbonic acid, formed when protons are buffered by bicarbonate, can be broken down into carbon dioxide and water. The former is excreted during respiration. The kidneys excrete excess acids primarily buffered with ammonia to form ammonium, though free protons are also excreted. Noncarbonic acids (such as the byproducts of amino acid metabolism — sulfuric and phosphoric acid) are also excreted by the kidneys. In the distal tubule, protons are secreted through production of titratable acid usually by buffering with phosphate.

## METABOLIC ACIDOSIS

Metabolic acidosis can be divided into two groups by the presence or absence of an elevated anion gap.

Anion gap = (measured anions) – (measured cations)

The major extracellular cation is sodium; the major extracellular anions are chloride and bicarbonate. If the anion gap is within normal limits (usually around 12 meq/L), it suggests that the acidosis results from bicarbonate losses from the gastrointestinal tract or kidneys. If the anion gap is elevated, it suggests the presence of an unmeasured acid.

1. Renal tubular acidosis (RTA)

   **Distal RTA, also known as *Type I RTA*, is the most common and clinically significant to urologists.** Distal RTA is a failure to excrete the appropriate amount of protons in the distal tubules leading to a nonanion gap metabolic acidosis. The urine pH may be greater than 5.5. Hypokalemia will often ensue. **Patients with distal RTA frequently have recurrent calcium phosphate urolithiasis. This occurs because acidosis leads to bone resorption, which increases the filtered load of calcium in the urine. Calcium-phosphate is less soluble in the alkaline urine of distal RTA, leading to nephrocalcinosis and stone formation. The treatment for distal RTA is to reduce the degree of acidosis with sodium bicarbonate, sodium citrate, or potassium citrate. Potassium citrate not only helps replace potassium losses but also inhibits stone formation.**

   Proximal RTA, also known as *Type II RTA*, is a failure of adequate reabsorption of bicarbonate in the proximal tubule. The distal tubule is then overwhelmed and is limited in its ability to reclaim the bicarbonate. Hypokalemic, nonanion-gap metabolic acidosis can occur but is usually self-limited because the distal tubule can fully absorb the filtered load of bicarbonate when the serum bicarbonate level falls to between 15 and 20 mEq/L. Urinary citrate levels are not reduced so there is no increased predilection for nephrocalcinosis and stone formation, despite increases in urinary calcium levels. The treatment for proximal RTA is oral sodium bicarbonate and potassium supplementation.

2. Metabolic alkalosis

   Metabolic alkalosis usually occurs in the setting of volume depletion. In these states, hypovolemia signals an increase in aldosterone levels, which causes sodium reabsorption and hydrogen secretion in the collecting duct. This can manifest as a paradoxical aciduria in patients with metabolic alkalosis. This condition is often called a *volume contraction alkalosis* and responds to intravenous normal saline. Volume-expanded alkalemic states (such as those associated with glucocorticoid or mineralocorticoid excess) are not fluid responsive.

## Other functions of the kidneys

### ERYTHROPOIESES

The kidney is also responsible for 90% of erythropoietin (EPO) production; the remaining 10% is from the liver. EPO is produced by interstitial fibroblastlike cells in the proximal tubules in response to low oxygen levels. Regulation of the EPO involves hypoxia-inducible factor-1 (HIF-1). HIF-1 levels are increased in hypoxic conditions but undergo ubiquitin-mediated degradation in nonhypoxic conditions. HIF-1 is implicated in the pathogenesis of renal cell carcinoma in von Hippel-Lindau disease and most sporadic renal cell carcinomas. The number of EPO-producing cells decreases in the setting of CKD because of interstitial fibrosis, hence the high prevalence of anemia within the CKD population.

### BONE MINERAL REGULATION

The kidney also plays a role in vitamin D regulation via the activation of 25-cholecalciferol by 1-alpha hydroxylase. Active calcitriol goes on to regulate calcium metabolism in the bone, intestine, parathyroid, and kidney. Parathyroid hormone increases calcium reabsorption in the distal tubule, decreases phosphate reabsorption in the proximal tubule through cotransporter inhibition, and increases levels of 1-alpha hydroxylase. Loop diuretics prevent the reabsorption of calcium in the loop of Henle, and loop diuretics may be given in addition to intravenous fluids for the treatment of hypercalcemia. On the other hand, thiazide diuretics increase the reabsorption of calcium and may be given to recurrent calcium stone formers for medical prophylaxis.

## *Self-Assessment Questions*

1. *What percentage of urinary creatinine is secreted? How does this change in worsening renal failure?*
2. *Besides using low or iso-osmolar contrast agents at reduced volumes, which additional measure is best for reducing risk of contrast-induced nephropathy (CIN)?*
   a. *Periprocedural IV hydration*
   b. *N-acetyl cysteine*
   c. *Sodium bicarbonate*
   d. *Steroid prep*
3. *What is the leading cause of death in patients with chronic kidney disease (CKD)?*

## SUGGESTED READINGS

1. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, et al: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, *Lancet* 375:2073–2081, 2010.
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## CHAPTER 25

# Renal Transplantation

Ali Naji, MD, PhD • Somnath Chattopadhyay, MD

## Indications

Renal transplantation is now regarded as the treatment of choice for a spectrum of pathology leading to end-stage renal disease (ESRD). **The three most common indications for renal replacement are insulin-dependent diabetes mellitus, glomerulonephritis, and hypertensive glomerulosclerosis.** Other causes of renal failure include polycystic kidney disease, systemic lupus erythematosus, Alport disease, Immunoglobulin A (IgA), nephropathy, obstructive nephropathy, recurrent pyelonephritis, nephrosclerosis, interstitial nephritis, and chronic calcineurin inhibitor-induced nephrotoxicity.

**Patients may be placed on the waiting list either upon initiation of chronic maintenance dialysis (defined as dialysis that is regularly furnished to an ESRD candidate) or when the creatinine clearance or glomerular filtration rate (GFR) is less than approximately 20 mL/min.**

**Preemptive transplantation, which predominantly is indicated for recipients who have a living kidney donor, has been shown in large studies to have significant patient and graft survival.** These results are postulated to be due to long-term cardiovascular effects of hemodialysis, lower rates of delayed graft function (DGF) and rejection seen in preemptive transplantation, and better socioeconomic and demographic features of the patient population able to opt for preemptive transplantation. However, preemptive transplants are still a small percentage of the total number of transplants, owing to a limited donor pool.

Although renal transplantation improves survival and quality of life for ESRD patients, a shortage of donor organs is the major limiting factor. Currently 97,503 are on a waiting list for a kidney; in 2012 only 16,485 patients received a kidney transplant.

# Immunological Barriers to Renal Transplant

## MAJOR HISTOCOMPATIBILITY ANTIGENS

**The major histocompatibility antigen complex (MHC) includes genes encoding the human leukocyte antigens (HLA) on chromosome 6.** The MHC molecules are transmembrane proteins that present peptide antigens to T lymphocytes and induce immune recognition.

Class I MHC is expressed on all cell types including lymphocytes and presents small peptide antigens derived from intracellular proteins. MHC Class I presentation is restricted to CD8-bearing T lymphocytes. MHC Class II expression is restricted to immune cells with antigen-presenting cell (APC) capacity (macrophages, dendritic cells, B lymphocytes), vascular endothelial cells, and some parenchymal cell types (enterocytes), and presents larger peptide antigens that are derived from the breakdown of exogenous peptides. MHC Class II presentation is restricted to CD4-bearing T lymphocytes.

MHC genes are expressed codominantly (a paternal and maternal allele of all MHC genes is equally expressed). Any two siblings have a 25% chance of being HLA identical and a 50% chance of sharing one haplotype. The importance of HLA matching on graft survival is well established, although even totally mismatched living donor transplants have a better outcome than deceased donor transplants.

## ALLOGRAFT REJECTION

The clinical manifestations of allograft rejection fall under three major categories: hyperacute, acute, and chronic.

1. Hyperacute rejection

   **Hyperacute rejection is caused by preformed antibodies against ABO or MHC antigens present on the endothelial cells.** This in turn leads to activation of the classic complement pathway. Complement components C3a and C5a attract inflammatory cells and platelets to the target sites, and component C5b-9 forms the membrane attack complex and damages the endothelium. Injury to the endothelial cells exposes the underlying matrix, and tissue factor is released which activates the extrinsic coagulation pathway. This leads to intravascular thrombosis, hemorrhage, and graft loss. Hyperacute rejection can be prevented by using ABO-compatible grafts and crossmatch testing for preformed anti-HLA antibodies.

2. Acute cellular rejection (ACR)

   **ACR is a T cell-mediated process.** T cells are activated via two different pathways: In the *direct pathway*, the donor MHC molecules on the donor APCs are recognized as "non self" by the recipient T cells, leading to an alloimmune response. In the *indirect pathway*, the alloimmune response is elicited by the recipient APCs presenting donor MHC antigens to recipient T cells. Histologically, ACR manifests as endotheliitis, tubulitis, and glomerulopathy and is usually reversible with intensification of immunosuppression.

3. Chronic rejection

   **Chronic rejection is the major cause of late renal allograft loss. The biology of chronic rejection is not fully understood.** It has been suggested that, in contrast to acute rejection, the indirect pathway, and alloantibodies and complement, may play dominate roles in chronic rejection. Chronic rejection is not reversible by intensification of immunosuppression.

## Immunosuppression

Immunosuppression after renal transplantation is divided into two phases: (1) induction, which is a period of high-dose immunosuppression in the perioperative period and (2) maintenance, which occurs posttransplant at lower doses for the life of the renal transplant.

The immunosuppressant drugs commonly used include:

1. Anti-T-cell antibodies (Thymoglobulin)

   Thymoglobulin is a polyclonal rabbit antihuman thymocyte antibody preparation. The purified IgG fraction contains antibodies directed against cell-surface molecules expressed on T lymphocytes, B cells, NK cells, and macrophages. Additionally, polyclonal antibodies cross-link the TCR, causing partial T-cell activation and blockade of T-cell proliferation. After administration, these antibodies cause rapid lymphopenia secondary to complement-mediated cell lysis and opsonization. A massive release of cytokines may occur, known as *cytokine release syndrome*, characterized by fevers, chills, dyspnea, bronchospasm, flash pulmonary edema, and central nervous system complications. Pretreatment with corticosteroids is recommended to reduce the incidence of this "cytokine storm."

2. Anti-IL2 receptor antibody (basiliximab)

   Basiliximab is a chimeric murine/human monoclonal antibody that binds to the IL-2 receptor alpha chain known as CD25, which expresses preferentially on activated T lymphocytes. It is used as an induction immunosuppression and is generally reserved for recipients who are at low risk of rejection (e.g., HLA identical donor).

3. Corticosteroids (prednisone)

   Corticosteroids are used as induction agents and in maintenance regimens. Corticosteroids in the form of prednisone are also the most common agents used for treatment of acute allograft rejection. Corticosteroids have a variety of antiinflammatory and immunomodulatory effects. Corticosteroids also impair monocyte and macrophage function and decrease the number of circulating CD4+ T cells. Adverse effects include diabetes, muscle loss, psychosis, cataracts, peptic ulceration, osteoporosis, and impaired wound healing. In renal transplantation, early withdrawal (within 3 months) is associated with an increased incidence of acute rejection; delayed withdrawal increases the risk of late acute rejection.

4. Calcineurin inhibitors (CNI) (cyclosporine and tacrolimus)

   Calcineurin is a calcium/calmodulin-dependent phosphatase which, when activated, leads to T-cell proliferation. Cyclosporine binds to cyclophilin, and tacrolimus to an intracellular binding protein named *FK506-binding protein (FKBP-12).* These CNI-immunophilin complexes inhibit calcineurin activity, preventing cytokine gene transcription. The net result is a blockade in the production of cytokines such as IL-2 and inhibition of T-cell activation and proliferation. Both tacrolimus and cyclosporine provide optimal immunosuppression and result in equivalent graft and patient survival. However, incidence of acute rejection episodes may be lower with a tacrolimus-only regimen when compared to a cyclosporine-only regimen.

   Many side effects of CNIs are dose related and include nephrotoxicity (which presents in the long term as interstitial fibrosis and fibrous intimal thickening), hypertension, neurotoxicity presenting as headache (more common with tacrolimus), tremors, agitations, psychosis and hallucinations, diabetes (more common with tacrolimus), hyperkalemia, hyperlipidemia, gingival hyperplasia, and hypertrichosis (specific for cyclosporine). Additionally, drugs that interact with CYP3A4 (e.g., antifungals) also affect the concentration of CNIs, which are metabolized by the cytochrome P450 3A4 enzyme in the gut and liver.

5. Mycophenolate mofetil (MMF) and mycophenolate sodium (MPS)

   MMF and MPS are rapidly converted in the liver to mycophenolic acid (MPA), which is the active compound. MPA preferentially blocks proliferation of activated lymphocytes. The main dose-related side effects of MPA are diarrhea, nausea, vomiting, and myelosuppression. Azathioprine is used by most centers in patients intolerant of MMF.

6. Mammalian target of rapamycin (mTOR) inhibitors (sirolimus)

   Sirolimus inhibits mTOR, which in turn blocks T-cell activation. It is not used in the perioperative period because of its profound inhibition of fibroblast activity, preventing wound healing. Important side effects of sirolimus include hypercholesterolemia, myelosuppression, mouth ulcers, interstitial pneumonitis, and poor wound healing. Sirolimus is metabolized by the cytochrome P450 3A4 enzyme and therefore has similar drug-drug interactions as CNIs.

## Recipient Evaluation

Prior to listing, all candidates undergo a rigorous medical, surgical, and psychosocial evaluation. All recipients with high risk of cardiac disease (diabetes mellitus, age older than 50 yrs, smoking) or previous coronary artery disease must be carefully evaluated to reduce the perioperative risk of mortality. **Depending on the type of malignancy, a 2- to 6-year cancer-free period is advised for patients with a past history of malignancy** because of the risk of recurrence under immunosuppression.

Surgical evaluation involves ruling out vascular or urologic issues to transplant. Patients with a history (claudication, rest pain) or signs (absent distal pulses, bruit) of peripheral vascular disease should be investigated by imaging studies (CT of the abdomen) and may require angioplasty prior to transplant.

Psychosocial evaluation is to ensure compliance with medications posttransplant. In patients with a prior history of noncompliance, a definite willingness to follow all medical advice is essential before listing for a transplant.

**Removal of native kidneys is rarely required in cases with large polycystic kidneys, chronic infection, or severe reflux disease.**

## Deceased Donor Kidney Allocation

In the United States, whenever a deceased donor kidney is available for donation, **blood group (ABO) compatible recipients are allocated organs on the basis of a point system composed of the following factors:**

1. Waiting Time: Patients with ESRD start accruing time from the time of listing (which can occur once their GFR is less than 20 mL/min, with or without being on maintenance hemodialysis).
2. HLA mismatch: Points are assigned to a patient based on the number of HLA mismatches between the donor and the recipient at the DR locus.
3. Panel reactive antibody (PRA): Calculated PRA (cPRA) is a calculation of the likelihood that the HLA antibodies of the recipient would be incompatible to the HLA specificities within the donor pool. Sensitized candidates with defined unacceptable HLA antigens that yield a cPRA of 80% or greater are assigned priority points.
4. Pediatric kidney transplant candidates: Organs from donors less than 35 years of age are prioritized for pediatric recipients.
5. Donation status: Prior organ donors developing ESRD receive priority points.

## Living Donor Evaluation

Evaluation of a potential living donor consists of detailed medical, psychosocial, and surgical evaluations.

Medical evaluation includes testing to evaluate fitness for surgery to reduce perioperative risks and to rule out conditions predisposing future kidney disease — poorly controlled hypertension, glucose intolerance, active or chronic viral illness (hepatitis B, hepatitis C, HIV), proteinuria or hematuria, and GFR less than 80 mL/min.

Psychosocial evaluation is to assess any active mental health issues, substance abuse issues, compliance with medications, and coercion to donate.

**Surgical evaluation includes** computed tomography (CT) and magnetic resonance (**MR**) **angiography to evaluate the kidney anatomy and define the surgical plan. Removing the donor's left kidney is preferred because of the length of the renal vein available for implantation;** however, in the case of significant size or function disparity, the optimal kidney is reserved for the donor.

## Living Donor Operation

### OPEN NEPHRECTOMY

The open technique is a well-proven procedure to safely procure kidneys from living donors. It remains the fallback procedure for patients with complex arterial anatomy and in laparoscopic cases in which difficulties are encountered intraoperatively.

Depending on which kidney is being removed, the donor is positioned in the right or left lateral decubitus. The incision extends from the tip of the twelfth rib to the lateral border of the rectus in the direction of the umbilicus. The muscular layers of the lateral abdominal wall are divided, and the peritoneum is identified and retracted medially to visualize the retroperitoneal space. The Gerota fascia is incised, and the kidney is separated from the surrounding perirenal fat. The ureter is identified below the lower pole of the kidney, running on the anterior surface of the psoas muscle, and traced to the pelvic brim. The renal vein is identified at its junction with the inferior vena cava (IVC) or where it lies anterior to the aorta, depending on whether the right or left kidney is being recovered, and then mobilized. In recovering a right kidney, the renal artery is identified in the retrocaval space; for the left kidney, the renal artery is identified to its origin from the aorta. The ureter is divided distally. The renal artery and vein are clamped and then divided. The kidney is removed and flushed with cold preservative solution through the renal artery until the effluent from the renal vein is cleared of blood.

### LAPAROSCOPIC DONOR NEPHRECTOMY

Most institutions now follow the laparoscopic approach for living donor nephrectomy. The laparoscopic approach can be hand assisted, purely laparoscopic, or robotic.

The hand-assisted approach consists of placing a 6.5- to 7-cm midline or Pfannenstiel incision for the hand port, a 10- to 12-mm incision just below or lateral to the umbilicus for the instrument port and a 5-mm incision 6 to 8 cm lateral to the umbilicus for the camera port.

For a left nephrectomy, after the creation of the pneumoperitoneum, the descending colon is mobilized from the splenic flexure to the pelvic rim in order to expose the Gerota fascia. Next, the left ureter and the gonadal vein are identified at the level of the iliac vessels. The gonadal vein is followed proximally to identify the left renal vein, which is exposed to the point it courses over the aorta. The left kidney is now separated from the Gerota fascia and the adrenal gland. The renal artery is identified from the posterior aspect after retracting the kidney medially. Once the kidney is fully mobilized, the donor is given diuretics to promote diuresis, and the ureter is divided. After systemic heparin administration, an endovascular stapler is used to divide the renal artery and then the renal vein, and the kidney is removed through the hand port site. The kidney is then flushed with cold preservative solution through the renal artery until the effluent from the renal vein is cleared of blood.

The purely laparoscopic approach has the advantage of a slightly smaller Pfannenstiel incision but lacks the tactile feedback in the hand-assisted approach and requires advanced laparoscopic training. The robotic approach has the advantage of 360-degree maneuverability and three-dimensional views but is expensive and time-consuming.

## Recipient Operation

### BENCHING OF THE KIDNEY

The first step in preparation of the kidney prior to implantation involves detailed inspection to rule out irreparable injury such as damage to the renal artery and to look for neoplasms. The next step is to dissect out the renal artery and vein to create suitable lengths for implantation and to ligate adrenal and gonadal branches. With a deceased donor kidney, a Carrel patch is created from the donor aorta for arterial anastomosis. Dissection deep to the hilum of the kidney should be avoided. Reconstruction may be required in the case of multiple renal arteries, a short right renal vein with IVC extension or duplicate ureters. The final step is to clean out the perirenal fat, taking care to preserve the fat around the lower pole of the kidney to avoid damage to the vascular supply to the ureter.

## TECHNIQUE OF RECIPIENT OPERATION

In a standard adult kidney transplant, the kidney is placed in a heterotopic position in the right or left retroperitoneal iliac fossa. The right iliac fossa is preferred because the iliac vessels are more superficial in their course on the right side. Intraperitoneal placement of the kidney is performed in the case of simultaneous pancreas-kidney transplants, previous kidney transplants (for access the proximal vessels), or small pediatric patients (less than 30 kg).

The standard incision is a “hockey stick” in the right or left lower quadrant, starting just above the pubic symphysis and extending along the lateral border of the rectus muscle. After incising the external oblique aponeurosis along the incision, the internal oblique and the transverses muscle fibers at the lateral border of the rectus muscle are separated in order to reach the retroperitoneal space. The peritoneum is swept medially in order to reach the psoas muscle and the iliac vessels. The lymphatic tissue along the external iliac artery and vein is ligated to prevent lymphocele. The external iliac artery and vein are dissected free from surrounding retroperitoneal fat, and dividing internal iliac vein branches may be required to achieve adequate exposure for implantation.

Implantation starts with the venous anastomosis, which is done in an end-to-side manner. Arterial anastomosis is performed in a similar end-to-side manner between the donor renal artery or Carrel patch and the recipient external iliac artery. Before the reperfusion, the recipient is given intravenous diuretics to promote diuresis. After reperfusion and hemostasis, the ureter is trimmed to get a well-vascularized segment and the end is spatulated. End-to-side ureteroneocystostomy is performed and a detrusor tunnel is created to prevent reflux. A ureteropyelostomy (dividing the native ureter) can also be utilized to establish the continuity of the genitourinary tract.

## Postoperative Management

In the absence of severe ischemic damage, a brisk diuresis is likely to begin within minutes of revascularization. Mild diuresis is reassuring and should be encouraged by replacement of urine volumes and, if necessary, by diuretics. Severe dehydration and electrolyte abnormalities can be the outcome of inadequate replacement of losses during a massive diuresis, especially in children. If diuresis continues, fluid replacement should lag behind the urine output, allowing gradual return to normal urine volumes over the next 12 to 24 hours.

## Postoperative Complications

### RENAL ARTERY THROMBOSIS

Sudden decrease or cessation of urine output after a period of brisk diuresis can be secondary to renal artery thrombosis. It is a rare (less than 1%) but devastating complication. **Renal artery thrombosis usually occurs because of intimal dissection or torsion of the vessels.** Diagnosis is made by color Doppler examination of the kidney, which may reveal high resistive indices and reversal of flow signal during diastole or absence of blood flow to the renal parenchyma. **Once diagnosis is made, immediate reexploration is indicated to salvage the kidney, but usually the graft is lost.**

### RENAL VEIN THROMBOSIS

Renal vein thrombosis **usually presents as swelling and tenderness over the kidney and hematuria.** Diagnosis can be made by color Doppler examination of the kidney**. Immediate thrombectomy can potentially salvage the kidney,** but usually diagnosis is delayed, making salvage of the graft not possible and requiring its removal.

### HEMORRHAGE

Hemorrhage may present as a drop in hemoglobin requiring blood transfusions, a sudden drop in urine output, or a rise in serum creatinine secondary to compression on the kidney or swelling at the incision site. Reexploration is indicated only if the hematoma is compressing the kidney or if blood loss continues, requiring multiple transfusions.

## ACUTE TUBULAR NECROSIS

**Acute tubular necrosis (ATN) occurs in up to 30% of renal transplants and primarily only occurs in deceased donor transplants.** Ischemia and reperfusion injury are the main precipitating factors. ATN presents as a drop in urine output after initial diuresis or failure to start making urine after reperfusion. Technical complications should be ruled out before making this diagnosis because **ATN in most cases is ultimately a self-correcting condition.**

## URINARY TRACT COMPLICATIONS

### Urinary Leak

**Urinary leak, or fistula, usually presents within a few days or weeks after the transplant and is secondary to distal ureteral devascularization.** Diagnosis is made by ultrasound of the kidney and analysis of the fluid collection for creatinine level, or by cystogram. **Small leaks can be managed by percutaneous nephrostomy and stenting. Large leaks and leaks discovered early after transplant require surgical correction (ureteroureterostomy, ureteropyelostomy, or revision of the ureteroneocystostomy).**

### Urinary Obstruction

**Early obstruction is usually due to a clot, hematoma, or kink in the transplant ureter. Late obstruction is secondary to ischemia and ureteral stricture leading to hydronephrosis, which is diagnosed by ultrasound.** Initial treatment usually consists of percutaneous nephrostomy with dilatation and stenting of the transplant ureter. Persistent strictures require surgery with ureteral reimplantation or ureteroureterostomy or ureteropyelostomy using the native ureter.

## LYMPHOCELE

Collection of lymph from the cut ends of the lymphatics along the iliac vessels can cause a mass effect on the kidney. **Incidence of lymphocele is between 1% and 15% in different series.** Asymptomatic lymphoceles can be observed. **Symptomatic lymphoceles need intervention in the form of percutaneous drainage with sclerotherapy or laparoscopic fenestration.**

## INFECTIOUS COMPLICATIONS

Infections in the first month posttransplant are usually caused by bacterial and fungal pathogens and include urinary tract infections, pneumonias, candidal infections, catheter-related infections, and intravenous line-related infections.

Opportunistic infections usually affect renal transplant recipients between 30 and 180 days after transplantation.

**Cytomegalovirus (CMV) is the most important viral pathogen and usually causes infection about 1 month posttransplant.** Its severity varies from mild fever to severe leukopenia, hepatitis, interstitial pneumonitis, GI ulceration, renal insufficiency, and bacterial or fungal infections. CMV infection also leads to opportunistic "super" infections such as pneumocystic carinii, Listeria, and aspergillus infection. CMV infection also has been postulated to have a role in early onset allograft rejection.

**Epstein-Barr virus (EBV)** infection may present as an uncomplicated mononucleosis syndrome characterized by fever, leukopenia, mild hepatitis, and atypical lymphocytosis with a negative heterophile test.

**Polyomavirus nephropathy (BK) virus persists in the kidney and sheds in the urine. It is an important cause of graft loss affecting 8% of transplant recipients.** Most patients with BK virus remain asymptomatic until they develop renal insufficiency. Some patients develop renal dysfunction secondary to ureteral stricture leading to hydronephrosis. Management is mainly based on judicious decrease in immunosuppression.

## MALIGNANCY

In renal transplant recipients, the reported incidence of 6% de novo malignant neoplasms represents a risk approximately 100 times greater than that in normal age-matched populations. The increased incidence of tumors appears to be related to the degree and duration of immunosuppression rather than to any particular agent.

**All transplant recipients have a disproportionately high (350 times higher) incidence of lymphomas known as posttransplantation lymphoproliferative disease (PTLD).** EBV is involved in the pathogenesis of PTLD, which may present as a polyclonal disease that runs a benign course to a monoclonal, rapidly progressive, malignant process that requires aggressive treatment and carries a poor prognosis. Clinical presentation involves tonsillitis, fever of unknown origin, weight loss, hepatocellular dysfunction, pulmonary infiltrates, focal gastrointestinal disease with bleeding or bowel perforation, brain lesions, and invasion of the allograft.

## Summary

Kidney transplantation is the standard of care for ESRD. With improvements in our understanding of transplant immunobiology, better perioperative care, better preservation of organs, and better immunosuppressants, the results of kidney transplants have improved greatly, with most centers reporting acute rejection rates of less than 20% within the first year and 1-year graft survival rates of greater than 90%.

Use of living donor organs has further improved results, with a 5-year patient survival rate of 90%. Even with improvement in hemodialysis techniques, kidney transplantation is associated with better patient survival and quality of life.

Expansion of the kidney donor pool through utilization of extended criteria (marginal) donors, promotion of living donation and national paired kidney exchanges may help bridge the gap between patients with ESRD and the availability of organs. However, scarcity of donor organs remains the major limiting factor.

### CLINICAL PEARLS

1. Renal transplantation has better survival compared to hemodialysis for patients of end-stage renal disease (ESRD).
2. Human leukocyte antigens (HLA)-matched kidneys show better survival. However, with improved immunosuppression, even HLA-unmatched kidneys have better survival than hemodialysis.
3. Crossmatching for donor-specific antibodies has essentially eliminated hyperacute cellular rejection.
4. Acute cellular rejection is most common in the initial postoperative period; hence the rationale for high immunosuppression.
5. Perioperative decrease in urine output should be investigated for technical causes such as renal artery thrombosis, renal vein thrombosis, and urinary leak before relating it to acute tubular necrosis.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What are the indications and contraindications for a kidney transplant?*
2. *What are the common manifestations of allograft rejection? What are the common immunosuppressants used to treat and prevent rejection?*
3. *What are the common perioperative complications after a kidney transplant? What is the management of renal artery thrombosis?*
4. *How is a living kidney donor selected? What are the steps to select laterality?*

### SUGGESTED READINGS

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## CHAPTER 26

# Renovascular Hypertension

Benjamin J. Herdrich, MD • Edward Y. Woo, MD • Based in part on a chapter in the previous edition by Jagajan Karmacharya, MD, Shane S. Parmer, MD, and Jeffrey P. Carpenter, MD

## Overview

Renovascular disease (RVD) encompasses a number of pathologies, including atherosclerotic renovascular disease (ARVD), fibrodysplastic lesions, developmental renal artery stenosis (RAS), renal artery aneurysms, renal artery dissections, embolic occlusion, Takayasu arteritis and giant cell arteritis, and transplant RAS. The presence of RAS may lead to renovascular hypertension (HTN) due to vasoconstriction and intravascular volume expansion. About 5% of all patients with HTN have RAS as the etiology. The principles of treatment for patients with renovascular HTN include controlling the blood pressure (BP), preventing cardiovascular complications, and preserving renal function. Medical management is the first line of treatment and should be instituted on all patients with renovascular HTN. Patients with RVD and uncontrolled HTN, declining renal function, or episodes of flash pulmonary edema may be candidates for renal revascularization. Most renal revascularization can be done with an endovascular approach utilizing angioplasty and stenting with surgical revascularization reserved for the few patients who cannot be treated endovascularly.

## Historical Overview

**A historical overview of Renovascular Hypertension is located online at www.ExpertConsult.com**

## Historical Overview

Bright from Guy's Hospital in London was the first to associate HTN and renal disease in 1836. The classic experiments of Goldblatt in 1934 clearly demonstrated that ischemia localized to the kidneys was sufficient to elevate BP, which, in its early stages, was unaccompanied by decreased renal function. Clinical evidence of the validity of Goldblatt's experiment came in 1938 when Leadbetter and Burkland cured sustained diastolic HTN in a 5-year-old boy by nephrectomy. Pathologic examination of the renal artery from this kidney revealed a lumen severely occluded by a mass of smooth muscle outlined by an elastic lamella representing fibromuscular hyperplasia (FMH). Evidence linking atherosclerotic obstruction of the renal arteries to HTN was described in 1937 by Moritz and Oldt, who described severe vessel obstruction in an autopsy series of chronic hypertensives. These findings set a trend toward many unfortunate nephrectomies over the next several years, until Smith in 1956 published a large series demonstrating only a 26% cure rate and questioned the use of unilateral nephrectomy for renovascular hypertension (RVH). It was the development of translumbar arteriography in the 1950s that opened the door to large-scale investigation, ultimately paving the way for the development of surgical techniques to treat renovascular hypertension. As endovascular techniques have developed, open surgery for this condition has decreased significantly. A number of clinical trials have compared endovascular renal revascularization with medical management. These studies have largely shown a modest improvement in hypertension for patients, but the effects on renal function and survival are less clear. Currently, endovascular or surgical treatment is reserved for a select group of RAS patients with HTN that cannot be adequately controlled with medical management alone, declining renal function, or flash pulmonary edema.

# Pathology

## GENERAL

1. **Significant RAS (greater than 60%) is usually required to cause renovascular HTN.**
2. **Atherosclerosis is the most common cause of RAS leading to renovascular HTN.**
3. **Longstanding intrarenal hypoperfusion is associated with irreversible nephrosclerosis and poor response to revascularization.**

## ETIOLOGY

1. **ARVD** is by far the most common etiology of RVD. Men are affected twice as often as women, reflecting the prevalence of arteriosclerosis in the male population. The frequency of renovascular atherosclerosis is more common in elderly patients and in patients with hypertension, coronary artery disease, peripheral vascular disease, and congestive heart failure (CHF). Most renovascular atherosclerotic lesions occur at the renal artery ostium of the aorta or within the first few centimeters of the main renal artery (Figure 26-1). These lesions often represent "aortic spillover" lesions and are a continuation of the atherosclerotic disease in the aorta as it enters the renal artery ostium (Figure 26-2). Many patients with ARVD have bilateral disease. Disease progression over time is common, especially for patients with HTN and atherosclerosis in other parts of the body. Despite this, progression to a complete renal artery occlusion occurs infrequently.
2. **Fibrodysplastic lesions** affect less than 0.5% of the general population. *Fibromuscular dysplasia* is the term used to refer to this group of nonatherosclerotic, noninflammatory pathology affecting medium-sized arteries, which often includes the renal arteries. Although uncommon, it is second only to atherosclerosis as the most frequent cause of renovascular HTN. These lesions are found in the distal two thirds of the renal artery and may involve segmental branches (Figure 26-3). FMD is divided into intimal, medial, and perimedial dysplasia.
    a. **Intimal dysplasia:** This process accounts for only 5% of renal artery fibrodysplastic lesions. It is seen more often in infants and younger adults. It is seen with equal frequency

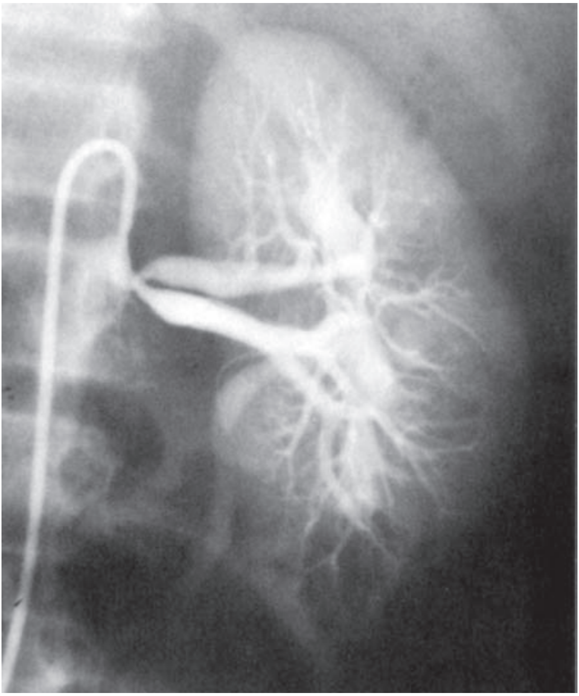

FIGURE 26-1 Aortogram of a 57-year-old woman with severe hypertension that displays a significant proximal left renal artery stenosis (RAS) consistent with atherosclerotic disease.

in both genders. It appears angiographically as a smooth focal stenosis of the main renal artery and rarely affects the segmental vessels. The etiology of this lesion is unknown, but it may represent focal proliferation of fetal arterial remnants within the vessel resulting in intimal hyperplasia. The media and adventitia are usually normal. Intimal fibroplasia can also be an acquired lesion after trauma or intraluminal injury to the vessel.

b. **Medial fibroplasia:** It is often part of a systemic arterial process involving the renal, carotid, and iliac arteries. This lesion accounts for 80% of renal artery fibrodysplasia, and it is four times more common in women than in men.

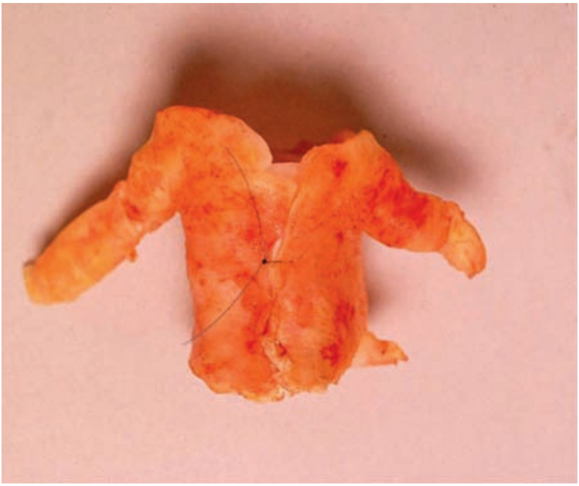

FIGURE 26-2 Operative specimen from transaortic endarterectomy demonstrating renal artery plaque (spillover lesions) contiguous with aortic disease. (From Seeger J: Renal and mesenteric disease. In Cronenwett JL, Johnston KW: *Rutherford's vascular surgery*, ed 7, Philadelphia, 2010, Saunders.)

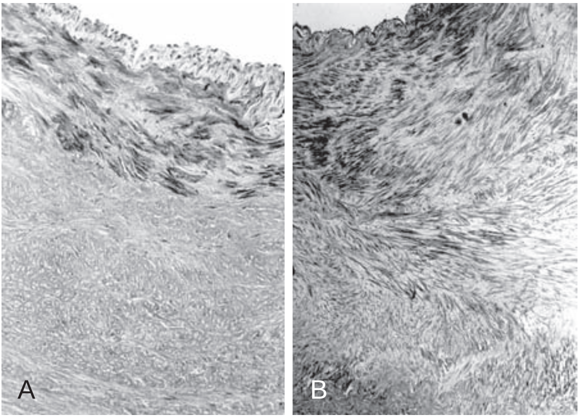

FIGURE 26-3 **A,** High-power photomicrographs demonstrating the appearance of a normal renal artery and tunica media. **B,** Vessel with fibromuscular hyperplasia (FMH) of the tunica media demonstrates overgrowth of the fibrous tissue and smooth muscle of that layer.

Although the lesion may be solitary, it is more commonly a series of stenoses with intervening aneurysmal dilations appearing as a string of beads on arteriography (Figure 26-4). It is bilateral in about 40% of patients. The lesions can extend into the segmental branches of the renal artery.

c. **Perimedial dysplasia:** This lesion accounts for 15% of renal artery fibrodysplasia. Almost all of these patients are women. These lesions affect the main renal artery as focal stenoses or multiple constrictions without mural aneurysms.

3. **Developmental RAS:** These failures of complete development of the renal artery account for approximately 40% of childhood renovascular HTN.

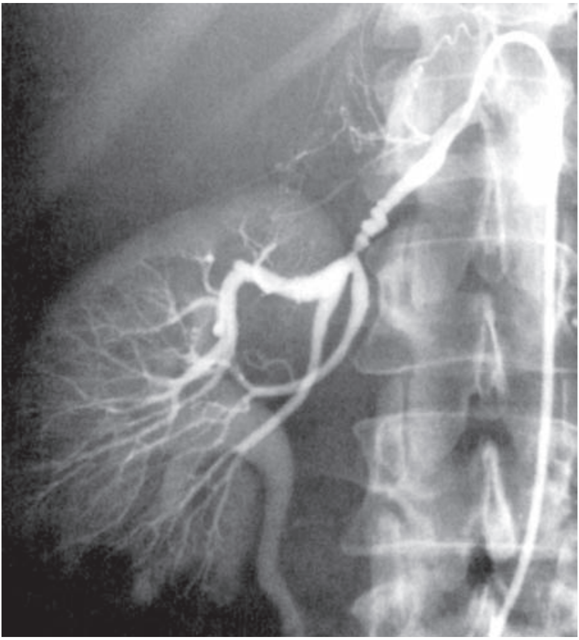

FIGURE 26-4 Renal arteriogram of a 60-year-old woman with hypertension (HTN) and postprandial pain who was found to have fibromuscular disease of both renal arteries and the superior mesenteric artery (SMA). The classic string-of-beads sign is demonstrated in the arteriogram.

4. **Renal artery aneurysm:** HTN is a common clinical presentation of renal artery aneurysm. The etiology of this HTN may be associated arterial stenosis, dissection of the artery, arteriovenous fistula formation, thromboembolism, or compression of arterial branches by the aneurysm.
5. **Renal artery dissection:** Patients with these lesions develop severe HTN as the kidney becomes ischemic. These lesions may be iatrogenic from catheter injuries or associated with trauma. They may occur spontaneously as a complication of underlying atherosclerotic or fibrodysplastic renovascular disease.
6. **Renal artery embolism:** Embolic occlusion of the renal artery is rare. The most common etiology is embolism from the left heart. These patients present with flank pain, HTN, and hematuria.
7. **Takayasu arteritis and giant cell arteritis:** Takayasu disease is common in Asia and affects younger women. Typically, the aorta and its distal branches are affected. RAS and renovascular HTN may occur, and the initial treatment is with steroid suppression supplemented with cytotoxic agents. Angioplasty and surgical revascularization are reserved for failure of medical therapy.
8. **Transplant RAS:** The stenosis is usually anastomotic in most instances; however, atherosclerosis, fibrous stricture, chronic rejection, and kinking may result in significant functional stenosis. The presentation varies from worsening or refractory HTN, insidious graft dysfunction, and volume overload (pulmonary edema).

## Pathophysiology of Renovascular Hypertension

### GENERAL

1. The renin-angiotensin-aldosterone system (RAAS) is important in maintaining blood volume, BP, and total body sodium.
2. RAS leads to renal hypoperfusion, activation of the RAAS, vasoconstriction, and volume expansion.
3. Continued activation of the RAAS can lead to remodeling of other organs such as the heart.

## FUNCTION OF THE RAAS (FIGURE 26-5) AND MECHANISM OF RENOVASCULAR HYPERTENSION

1. Renin is a proteolytic enzyme that is released from the granules of the juxtaglomerular apparatus (JGA) in response to changes in the pressure of the afferent arteriole.
2. Renin catalyzes the cleavage of angiotensinogen to produce angiotensin I, which is then proteolytically converted by angiotensin-converting enzyme (ACE) to angiotensin II, an extremely potent vasoconstrictor. This occurs in the plasma but also locally within many organs such as the kidney, heart, lung, and brain.

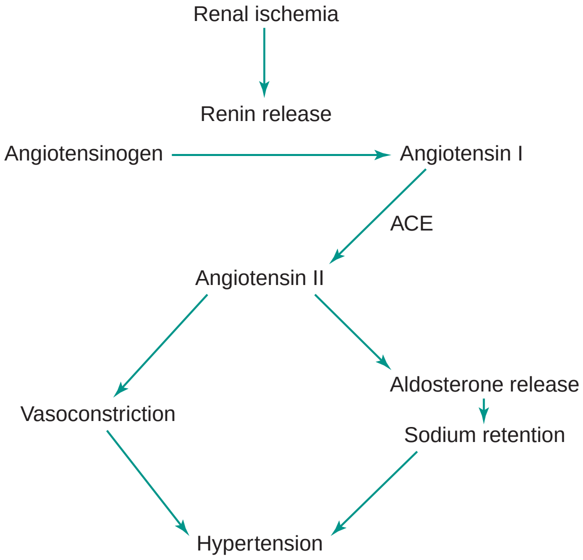

FIGURE 26-5 Renin-angiotensin-aldosterone system (RAAS). Renin is released from the granules of the juxtaglomerular apparatus in response to changes in the pressure of the afferent vessels. Renin acts on angiotensinogen to produce angiotensin I, which is converted to angiotensin II (needs angiotensin-converting enzyme [ACE]). Angiotensin II, a potent vasoconstrictor, releases aldosterone from the adrenal cortex potentiating sodium resorption and potassium excretion.

3. Angiotensin II also affects the release of aldosterone from the adrenal cortex, which potentiates sodium reabsorption and potassium excretion in the distal renal tubule.
4. Angiotensin II activates the G-protein coupled receptor angiotensin type 1 receptor (ATR1). Activation of ATR1 leads to vasoconstriction, upregulation of other endogenous vasoconstrictors, and increased sodium absorption by the kidney.
5. **Initially, the mechanism of renovascular HTN involves both the vasoconstrictive effects of angiotensin II and aldosterone-mediated volume expansion.**
6. Local paracrine effects of increased endothelin production, renin-angiotensin-aldosterone activation, oxidative stress, and structural remodeling of the heart and arteries are responsible for sustained HTN.
7. **If RAS is unilateral, the contralateral kidney can alter its sodium resorption to compensate for the diseased kidney and lessen the degree of volume expansion. If RAS is bilateral or present in a solitary kidney, this compensatory mechanism is eliminated leading to "volume-dependent" or Goldblatt hypertension.**

## Clinical Presentation

Distinctive clinical features that enable the clinician to make the diagnosis of renovascular HTN do not exist; however, the following findings in both the history and physical examination may lead one to suspect RVH.

1. Uncontrolled hypertension despite multiple antihypertensive medications
2. Hypertension in young women and children
3. Sudden onset of hypertension
4. Severe hypertension after age 55
5. Development of renal failure when treated with an angiotensin-converting enzyme inhibitor (ACEI)
6. An abdominal bruit
7. Acute flash pulmonary edema in the absence of acute coronary events
8. Uncontrolled HTN and declining renal function

## DIFFERENTIAL DIAGNOSIS

When evaluating a patient for renovascular HTN, other possible causes of HTN should be considered. A patient could potentially have asymptomatic RAS and a separate disease process as the etiology for HTN. While an exhaustive workup is not necessary for every patient, the following conditions should be considered in the differential diagnosis.

1. Coarctation of the aorta: This is a cause of HTN in children and young adults. The young patient age, a pulse differential between the brachial and femoral arteries, and a history of claudication would suggest this as a diagnosis.
2. Cushing syndrome: Glucocorticoid excess will often cause a typical appearance including centripetal obesity, moon faces, buffalo hump, and purple striae. Night salivary cortisol, urinary cortisol, and a low-dose dexamethasone suppression test can help establish a biochemical diagnosis.
3. Essential hypertension: Primary HTN represents the major etiology of HTN. In the absence of evidence of secondary causes, the patient is considered to have essential HTN. Clues that point to a specific secondary etiology should be investigated.
4. Hyperthyroidism or hypothyroidism: Patients may report symptoms of thyroid hormone deficiency or excess. TSH and free T4 are common blood tests that can accurately establish or rule out the diagnosis.
5. Oral contraceptives or other medication-induced hypertension: Cessation of medications causing HTN should result in normalization of blood pressure (BP).
6. Pheochromocytoma: Patients report episodes of palpitations, diaphoresis, and severe headache. A biochemical diagnosis of pheochromocytoma can be established if there is elevation of the plasma fractionated metanephrines, urinary metanephrines, or urinary catecholamines.
7. Primary aldosteronism: Elevation of the plasma aldosterone concentration with suppression of the plasma renin activity establishes a biochemical diagnosis of primary aldosteronism. Cross-sectional imaging and renal vein sampling can localize the source and differentiate between adrenal adenoma and adrenal hyperplasia.
8. Primary hyperparathyroidism: Hypercalcemia, mood disturbances, and a history of kidney stones can suggest hyperparathyroidism.
9. Primary kidney disease: This can be difficult to differentiate from renovascular HTN, but the absence of renovascular disease, elevated creatinine, abnormal urinalysis, and imaging demonstrating renal parenchymal disease can suggest this diagnosis.
10. Obstructive sleep apnea; Patients report a history of snoring at night and fatigue during the day. Obesity is often present in these patients.

## Diagnostic Studies

### GENERAL

Renal artery angiography has been the gold standard for imaging the renal arteries. Less invasive imaging options are now available to demonstrate the presence of RAS. These include renal duplex ultrasonography, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA). The presence of RAS alone does not make the diagnosis of renovascular HTN. Other functional tests can help to define when RAS is the etiology of HTN, including radionuclide renography and renal vein renin assays.

### SPECIFIC TESTS

1. Laboratory Tests
   a. Serum blood creatinine (Cr), blood urea nitrogen (BUN), sodium, potassium, bicarbonate, and chloride should be ordered on all patients suspected to have renovascular HTN. RAS can lead to renal hypoperfusion and impaired renal function. It is important to look for evidence of renal insufficiency because it will have an impact on the choice of imaging tests and impact treatment decisions.
   b. Peripheral plasma renin activity can be measured, but it is often not particularly useful. It is frequently normal despite the presence of renovascular HTN and can be elevated in a large number of patients with essential HTN. When plasma renin activity is measured under strictly controlled conditions (salt and volume restriction, antihypertensive medications withdrawn), most patients who are known to have renovascular HTN will demonstrate an elevated secretion of renin.
   c. Plasma aldosterone can rule out the diagnosis of aldosteronoma as an alternate cause of HTN.
   d. Plasma or urine metanephrines can rule out the diagnosis of pheochromocytoma as an alternate cause of HTN.
2. Imaging studies
   a. **Duplex ultrasonography** is the primary method of screening for RAS in many centers because it is safe and accurate. The sensitivity and specificity are greater than 90% when done by an experienced vascular lab. It also avoids exposure to nephrotoxic contrast agents and ionizing radiation. The degree of stenosis can be determined by measuring the peak systolic velocity (PSV) in the main renal artery. A PSV

greater than 180 cm/sec is usually consistent with hemodynamically significant RAS. Duplex ultrasonography can also measure both the kidney length and resistive index (RI). A RI greater than 0.8 or a renal length less than 7 cm are suggestive of significant intrarenal disease that may not be corrected by renal revascularization. The drawbacks of duplex ultrasonography include difficulty imaging the renal artery in obese patients and less anatomic detail for surgical planning than is offered with CTA or MRA.

b. **CTA is noninvasive and widely available, allowing accurate diagnosis of RAS and 3-D reconstruction of the arterial anatomy, which can be helpful in the event that revascularization is being considered.** Sensitivity and specificity for CTA has been reported as greater than 90% in a number of series. It also allows for imaging of the intraabdominal organs, which can not only provide clinical information about associated renal disease but also help assess for other etiologies of HTN (i.e., functional adrenal adenoma). The disadvantages of CTA are the risks associated with nephrotoxic contrast administration and exposure to ionizing radiation.

c. **MRA** offers many of the same advantage of CTA, including high degree of sensitivity and specificity for RAS, 3-D reconstruction of the arterial anatomy, and imaging of the kidneys and other abdominal organs. It does not carry the risks of ionizing radiation or contrast-induced nephropathy. However, **the contrast agent gadolinium is contraindicated in patients with severe renal impairment** (glomerular filtration rate **[GFR] less than 30 mL/min**) **due to the risk of nephrogenic systemic fibrosis** (**NSF**)**.** Other limitations include patients with claustrophobia or metal implants, which are either at risk of moving with the magnetic field or will limit the image quality because of artifact.

d. **Conventional angiography** requires obtaining arterial sheath access, usually either the common femoral artery or left brachial artery. A catheter is then positioned in the aorta at the level of the renal arteries. A contrast injection and imaging with a fluoroscopy machine capable of digital subtraction angiography (DSA) provides high quality images of visceral aorta and renal arteries and is the gold standard for diagnosing RAS. Additional techniques can be used to better define a renal artery lesion, including superselective angiography of the renal artery and segmental branches and pressure transduction across a visualized lesion. Furthermore, if a lesion is identified, it can usually be treated at that time. DSA does carry the risk of arterial access-related complications, such as thrombosis or pseudoaneurysm formation at the sheath site, dissection of the access vessels, and embolism (including embolic stroke if the brachial approach is utilized). It also carries the risk of contrast-induced nephropathy; however, carbon dioxide ($CO_2$) has been used in place of iodinated contrast agents to minimize this risk.

3. Functional studies
    a. **Radionuclide renography is a nuclear medicine method for quantifying split renal function.** A radiolabeled molecule is given, and the uptake and excretion by each kidney is imaged and quantified. This can be used to follow renal function over time. **In the presence of significant RAS, abnormal uptake and excretion may be seen on the affected side.** However, due to compensatory vasoconstriction of the efferent arterioles, renography may also be normal in the presence of RAS. A technique referred to as *captopril renography* can be used to help demonstrate the presence of renovascular HTN. Renography is repeated after the administration of an ACEI. This blocks the angiotensin II-mediated efferent arteriole vasoconstriction, thus blocking the kidney's natural compensatory mechanism. This will be seen as a decrease in radioisotope uptake and excretion by the kidney following ACEI administration. Normal captopril renography essentially rules out renovascular HTN. A positive test is suggestive of a renal etiology for HTN but is not specific to RAS because parenchymal disease can lead to false-positive results.
    b. **Renal vein renin assays are occasionally used to demonstrate that a known unilateral RAS is associated with increased renin production from the ipsilateral kidney.** This is an invasive test whereby the renal veins and the inferior vena cava (IVC) are catheterized percutaneously. Renal vein renin activity from each renal vein is compared to that drawn from the IVC. A ratio of renal vein renin to IVC renin greater than 1.5 is considered positive if it correlates with the side of the known RAS. Medications and sodium intake can affect renin production and thus the results of the study. Antihypertensive medications ideally should be stopped and sodium restricted prior to the study.

# Medical Therapy

## GENERAL

The goals of medical therapy are control of HTN, preservation of renal function, and prevention of cardiovascular events.

## METHODS OF MEDICAL CONTROL

1. Lifestyle modification including reduction of salt intake, weight loss (goal body mass index (BMI) less than 25 kg/$m^2$), and smoking cessation is an integral part of controlling HTN and minimizing the risk of cardiovascular events.
2. **Antiplatelet therapy** for secondary prevention of cardiovascular disease in patients with atherosclerotic RVD should include low-dose aspirin daily.
3. **Lipid lowering therapy aimed at preventing cardiovascular events should include a statin in patients with atherosclerotic RVD.** Lipid goals for this patient population generally include LDL-C less than 100 mg/dL (less than 70 mg/dL in patients at very high risk for cardiovascular events).
4. **Antihypertensive therapy to a goal BP of less than 130/80 mm Hg should be undertaken with blockade of the RAAS with either an ACEI or an angiotensin-receptor blocker (ARB) as first-line agents.** However, these drugs should be started in low doses; renal function should be assessed in 3- to 5-day intervals and the drug increased in gradual increments because they may reduce renal function in severe or bilateral RAS. If renal function is negatively impacted by ACEIs or ARBs, the creatinine levels return to baseline when these drugs are stopped.
5. Multidrug therapy is often needed to achieve BP control. Beta-blockers, alpha-blockers, calcium channel blockers, angiotensin II inhibitors, vasodilators, and diuretics are some common classes of antihypertensives used.

# Renal Revascularization

## GENERAL

1. The first operation described for renovascular HTN was a unilateral nephrectomy. This is rarely done today because it was shown to have a low HTN cure rate and it sacrifices the kidney.

2. Renal revascularization offers the possibility of improving blood flow to a hypoperfused kidney. Ideally, this will lead to decreased renin production by the affected kidney, improved BP control, normalization of the intravascularization volume with improved CHF and pulmonary edema, and improved kidney function.
3. Current options for renal revascularization include endovascular (i.e., angioplasty with or without stenting) and open (i.e., bypass, endarterectomy, heterotopic renal autotransplantation) techniques.
4. As technology has progressed, more patients are able to be treated with an endovascular approach, thus decreasing the number of open renal revascularization procedures performed.

## PTA AND STENTING (FIGURE 26-6)

1. General
   a. Renal artery percutaneous transluminal angioplasty (PTA) +/- stenting offers a minimally invasive approach to correcting RAS.
   b. Clinical trials have looked at multiple end points following renal artery PTA +/- stenting, including BP control, number of antihypertensive medications, renal function, and overall survival.
   c. Renal artery lesions in the midportion of the main renal artery and those in patients with FMD can often be treated with PTA alone. Atherosclerotic ostial lesions will generally require PTA with stent placement.
   d. Renal artery PTA +/- stenting is a very reliable method for correcting RAS with a low morbidity and mortality. Despite improved renal blood flow following renal artery PTA +/- stenting, many patients will not realize a change in their clinical condition. Therefore it is offered to a select group of patients who are most likely to benefit from the procedure.
2. Patient selection
   a. Patients with RAS greater than 60% should generally be offered PTA +/- stent when technically feasible and when one of the following conditions is met: uncontrolled HTN despite medical management, HTN with flash pulmonary edema or CHF, or worsening renal insufficiency.
   b. **Patients with FMD are generally treatable with PTA without stent because the lesions are typically in the distal**

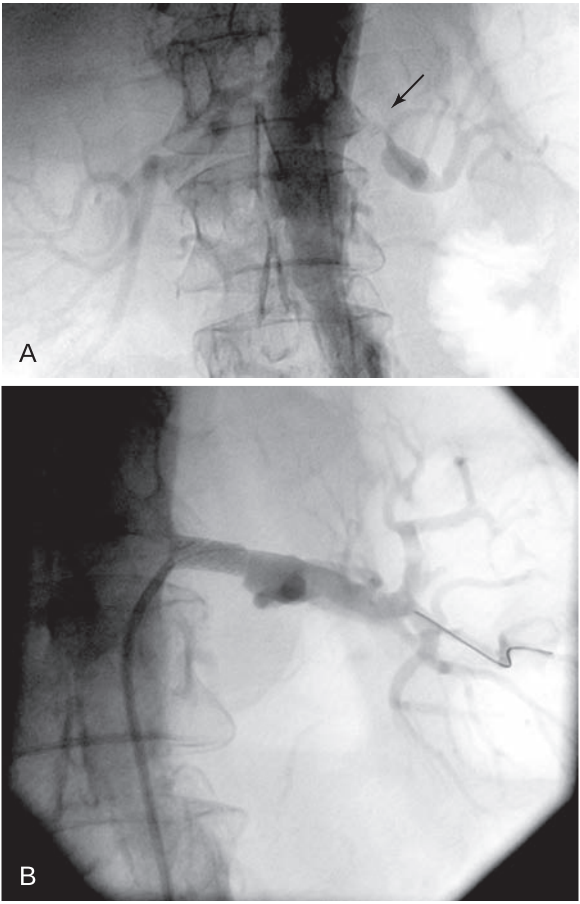

FIGURE 26-6 **A,** Renal arteriogram of a 66-year-old man demonstrating severe stenosis *(arrow)* of the left renal artery due to atherosclerosis. Note the post-stenotic dilatation. **B,** Angiogram showing the successful result after percutaneous angioplasty and stenting.

**portion of the renal artery, and lesions are fibrous (rather than calcified) and easily stretched open with PTA.**

c. **Patients with an RI greater than 0.8 or a renal length less than 7 cm generally have a poor response to renal revascularization because of significant intrarenal disease.**

3. Results
    a. The technical success of PTA +/- stenting to treat RAS is approximately 95%.
    b. Mortality rate is about 1%. The major complication rate is between 5% and 10%. The most common complications include acute renal failure, peripheral embolization, hematoma, pseudoaneurysm, and vessel damage at the femoral artery catheterization site.
    c. Restenosis rates after PTA and stenting for atherosclerotic RAS is about 10% at 9 months. Stenting, especially for atherosclerotic ostial lesions, has been shown to improve patency over PTA alone.
    d. In FMD patients, restenosis rates after PTA alone have been reported as 7% to 23% at 1 year, and about 80% of patients have improved or cured HTN at 1 year.
    e. **Randomized trials comparing renal artery PTA +/- stenting plus medical management with medical management alone have shown, at best, only a modest improvement in hypertension and no effect on renal salvage, cardiovascular events, or survival.**
    f. It is not clear whether negative randomized trials looking at PTA +/- stenting versus medical management in the treatment of RAS is due to lack of efficacy or poor selection of patients who will benefit from renal revascularization.

## SURGICAL THERAPY

1. General
    a. The goals of surgical intervention include the cure of HTN and the preservation of functional renal tissue.
    b. **The recent advances in endovascular techniques have dramatically decreased the number of open renal revascularization procedures performed.**
2. Patient selection
    a. Patients with RAS not amenable to endovascular treatment should be considered for surgical revascularization if they have uncontrolled HTN despite medical management, HTN with flash pulmonary edema or CHF, or worsening renal insufficiency.
    b. The following situations are difficult to treat with an endovascular approach. Patients with renovascular HTN

and these conditions should be considered for open surgical revascularization: renal artery aneurysm, simultaneous abdominal aortic aneurysm, multiple branch lesions, renal artery dissection, renal artery occlusion, or severe occlusive disease involving the visceral aorta.

   c. Patients with renal artery aneurysms greater than 2 cm should be offered open repair to prevent rupture.
   d. Nephrectomy for renovascular HTN is rare but can be considered when the renal disease is unreconstructable and the function of the affected kidney is less than 10%.

3. Surgical procedures
   a. Aortorenal bypass
      1) Reversed or nonreversed vein grafts from the infrarenal or supraceliac aorta may be used to bypass a region of RAS. The distal anastomosis is done in an end-to-end fashion because end-to-side anastomoses have the potential for competitive flow and propagation of thrombus into the renal artery.
      2) Prosthetic grafts are reserved for patients who have no suitable autogenous vein because these grafts have decreased patency rates compared with autogenous material.
      3) The supraceliac aorta, which is usually relatively spared of diffuse atherosclerotic disease, may be used for the proximal anastomosis if the infrarenal aorta is unsuitable.
   b. Aortorenal endarterectomy may be performed through an aortic incision. This technique is suited to treatment of ostial lesions, directly removing the diseased intima and plaque.
   c. Renal artery reimplantation may be performed for ostial lesions. The renal artery is dissected free, transected, and reimplanted into the aorta, usually at a more distal level.
   d. Alternative renal-artery reconstructive techniques may be used in specific clinical situations to avoid a diseased or otherwise unsuitable aorta as an inflow vessel.
      1) Hepatorenal bypass
      2) Splenorenal bypass
      3) Iliorenal bypass
      4) Mesorenal bypass

  e. Heterotopic autotransplantation of the kidney to the iliac artery and vein, thus relocating the kidney to the iliac fossa is an effective alternative method of renal revascularization.
  f. In ex vivo arterial repair, the kidney is removed from the patient allowing precise reconstruction of the renal vessels under ex vivo conditions of exposure, illumination, and magnification. This allows for precise reconstruction of complex lesions. The kidney may be replaced back into the renal fossa or autotransplanted to the iliac fossa (Figure 26-7).
4. Results
  a. The rate of restenosis following open surgical renal revascularization is less than 5% over 2 years.

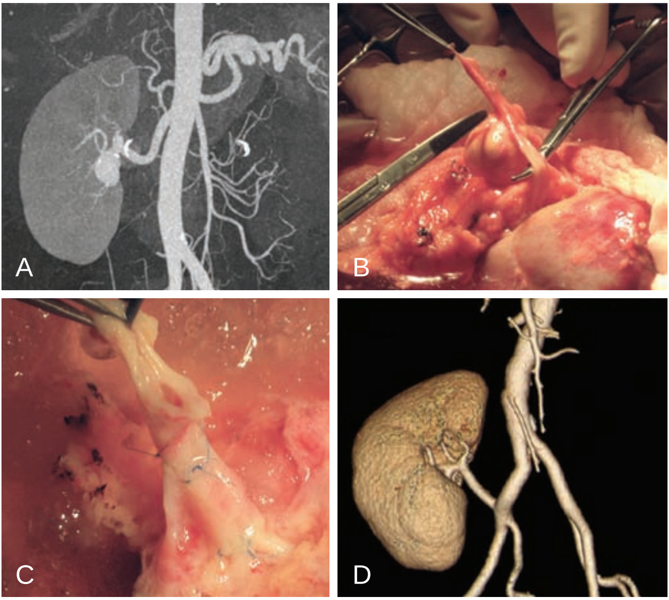

FIGURE 26-7 **A,** Computed tomographic angiography (CTA). **B,** Operative images of a large renal artery aneurysm is involving the segmental renal arteries. **C,** The patient underwent ex vivo repair. **D,** Heterotopic autoplantation relocating the kidney to the iliac fossa.

b. **In selected series, 85% of patients undergoing surgical renal revascularization either have been cured or have improved HTN.**
c. **Mortality of open renal revascularizations is about 1% to 3% and depends on the extent of the operation. The rate of major morbidity with open renal revascularization is about 20%.**
d. Patients with severe hypertension and declining renal function preoperatively may realize improved renal function after open renal revascularization. Some patients may even be liberated from dialysis.
e. **Patients who are cured of HTN following open renal revascularization have an improved dialysis-free survival.**

## Recommendations

Randomized controlled trials have failed to show significant benefit of PTA +/- stenting over medical therapy in the treatment of renovascular HTN. Specifically, a modest improvement in HTN may follow endovascular renal revascularization, but little evidence demonstrates improved renal function, decreased cardiovascular events, or improved survival. This, however, does not exclude the possibility that certain patients with renovascular HTN may benefit from renal revascularization. **A large retrospective series looking at surgical renal revascularization suggests that patients with severe hypertension and declining renal function derive the most benefit from revascularization, and some patients have even been liberated from dialysis. At this time, patients with severe RAS (greater than 60%) and HTN should only be considered for renal revascularization if there is failure of medical management to control the HTN, evidence of volume overload producing CHF or flash pulmonary edema, or declining renal function.** An endovascular method of renal revascularization should be utilized when possible given the high degree of technical success and the low associated morbidity and mortality. Patients who are not candidates for endovascular treatment should be considered for open surgical revascularization. Our approach to renovascular disease is outlined in the algorithm in Figure 26-8.

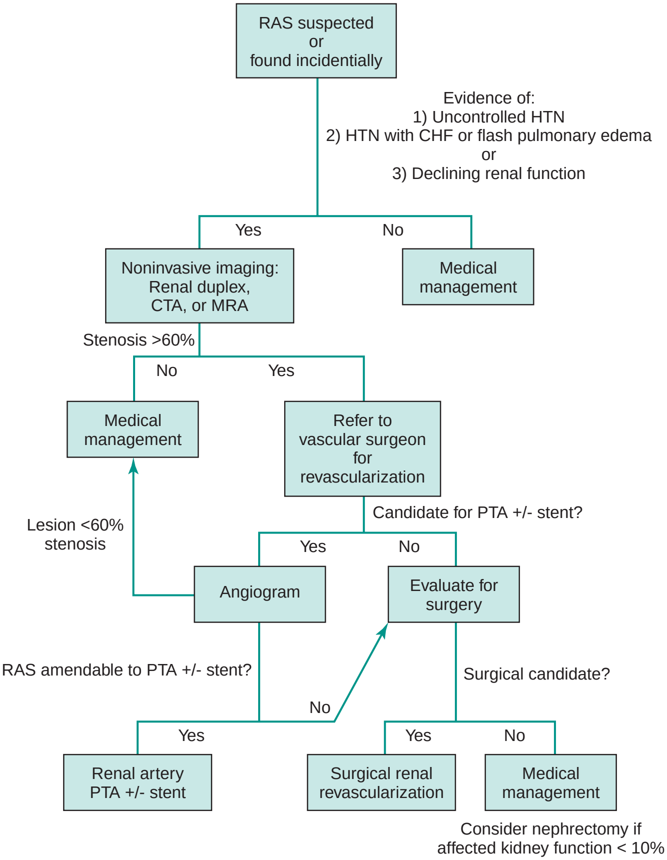
RAS suspected or found incidentally
Evidence of:
1) Uncontrolled HTN
2) HTN with CHF or flash pulmonary edema
or
3) Declining renal function
Yes
No
Noninvasive imaging: Renal duplex, CTA, or MRA
Medical management
Stenosis >60%
No
Yes
Medical management
Refer to vascular surgeon for revascularization
Lesion <60% stenosis
Candidate for PTA +/- stent?
Yes
No
Angiogram
Evaluate for surgery
RAS amendable to PTA +/- stent?
Surgical candidate?
No
Yes
Yes
No
Renal artery PTA +/- stent
Surgical renal revascularization
Medical management
Consider nephrectomy if affected kidney function < 10%

FIGURE 26-8 The workup and treatment algorithm for a patient with suspected or incidentally found renal artery stenosis (RAS).

## Conclusions

1. Most patients with renovascular hypertension can be managed medically.
2. Patients showing the most benefit from either endovascular or open surgical renal revascularization are those with severe hypertension, volume overload, and declining renal function.
3. When renal revascularization is indicated, an endovascular approach is preferred.

## CLINICAL PEARLS

1. Renovascular hypertension (HTN) is one of the most common causes of secondary HTN.
2. Increased renin production by a hypoperfused kidney leads to vasoconstriction and volume expansion because of activation of the renin-angiotensin-aldosterone system (RAAS).
3. Patients who benefit most from renal revascularization have severe hypertension, volume overload, and declining renal function.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What is the most common cause of renovascular hypertension (HTN)?*
2. *What is the workup for patients suspected of having renovascular HTN?*
3. *What is the initial management?*
4. *What are the indications for treatment of renal artery stenosis (RAS)?*
5. *What are the current revascularization options?*

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## CHAPTER 27

# Disorders of Sexual Development

Thomas F. Kolon, MD

The first sections of this chapter provide a basic template for the etiology of DSD. However, it may be worthwhile to read the history, physical exam, and evaluation descriptions first and then begin again with the start of the chapter to keep this subject in perspective. **The important issue with any DSD evaluation is not to get overwhelmed by the enormity of the differential diagnosis possibilities. Instead, work slowly through the differential diagnosis pathway** (see Differential Diagnosis, Page 2) **based on the physical exam and laboratory findings. Many possible diagnoses will remove themselves from contention in this manner.**

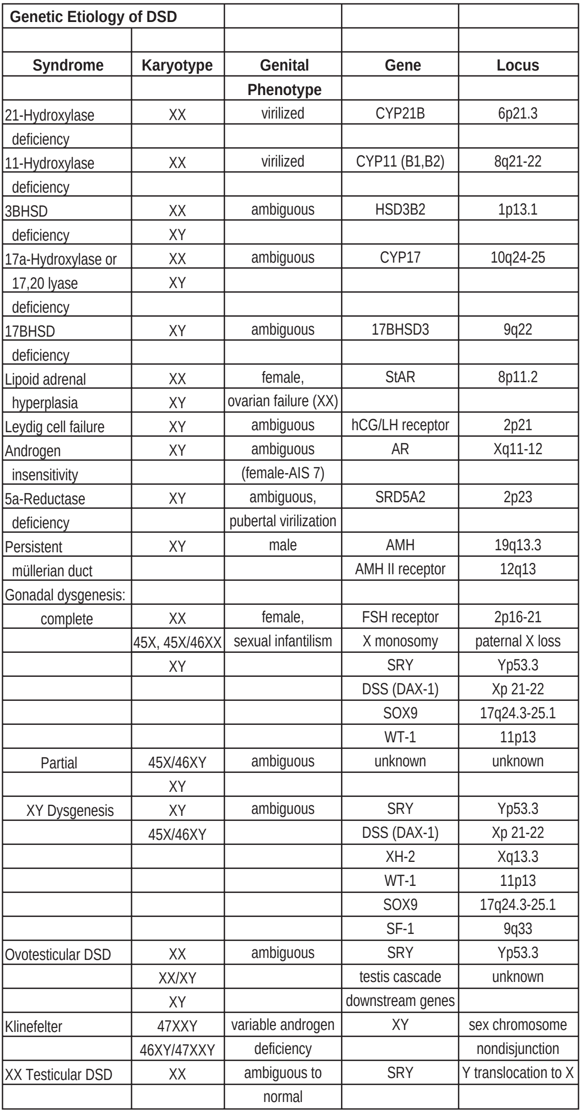
## 46XX DSD (Previously Called *Female Pseudohermaphroditism*)

46XX DSD, previously known as *female pseudohermaphroditism*, is the most common DSD. The ovaries and müllerian derivatives are normal and the sexual ambiguity is limited to masculinization of the external genitalia. A female fetus is masculinized if exposed to androgens, and the degree of masculinization is determined by the stage of differentiation at the time of exposure. Masculinization can occur secondary to exogenous maternal steroids as well.

**Congenital adrenal hyperplasia** (CAH) **accounts for the majority of 46XX DSD patients.** Inactivating or loss of function mutations in five genes involved in steroid biosynthesis can cause CAH: CYP21, CYP11B1, CYP17, HSD3B2, and StAR (Box 27-1). Although all six of these biochemical defects are characterized by impaired cortisol secretion, only CYP21 and CYP11B1 are predominantly masculinizing disorders (HSD3B2 to a lesser extent). Although the female fetus is masculinized due to overproduction of adrenal androgens and precursors, affected males have no

Human sex development occurs in an organized, sequential manner. Chromosomal sex is established at fertilization, which then directs the undifferentiated gonads to develop into testes or ovaries. Phenotypic sex results from the differentiation of internal ducts and external genitalia under the influence of hormones and transcription factors. When discordance occurs among these three processes (i.e., chromosomal, gonadal, or phenotypic sex determination), then disorders of sex development (DSD) develop. This has previously been termed *intersex* or *intersexualty*, but the new nomenclature has ended the use of the term *intersex* and now refers to it as *DSD*. Sexual differentiation is regulated by more than 50 different genes on both the sex chromosomes and autosomes. These genes encode transcription factors, gonadal steroid and peptide hormones, and tissue receptors. The sex determination genetic cascade involves the *SRY* gene (sex-determining region on Y) as the testis-determining factor, although other upstream (*SF1, WT1*) and downstream (*DAX1, SOX9, Wnt4, AMH,* homeobox) genes are also likely involved (see Figure 27-e1).

A failure of testis determination will usually result in the development of the female phenotype, although recent research has shed light on genes that are required in the female pathway, thus eradicating the theory that this is simply a “default” pathway. Genetic alterations resulting in partial testicular development can give rise to a wide spectrum of masculinization. In addition to defects in peptide hormones and their receptors, timing of hormonal exposure is also critical to appropriate development. Although much work remains to be done, recent advances in our knowledge have begun to unravel the molecular basis of DSD.

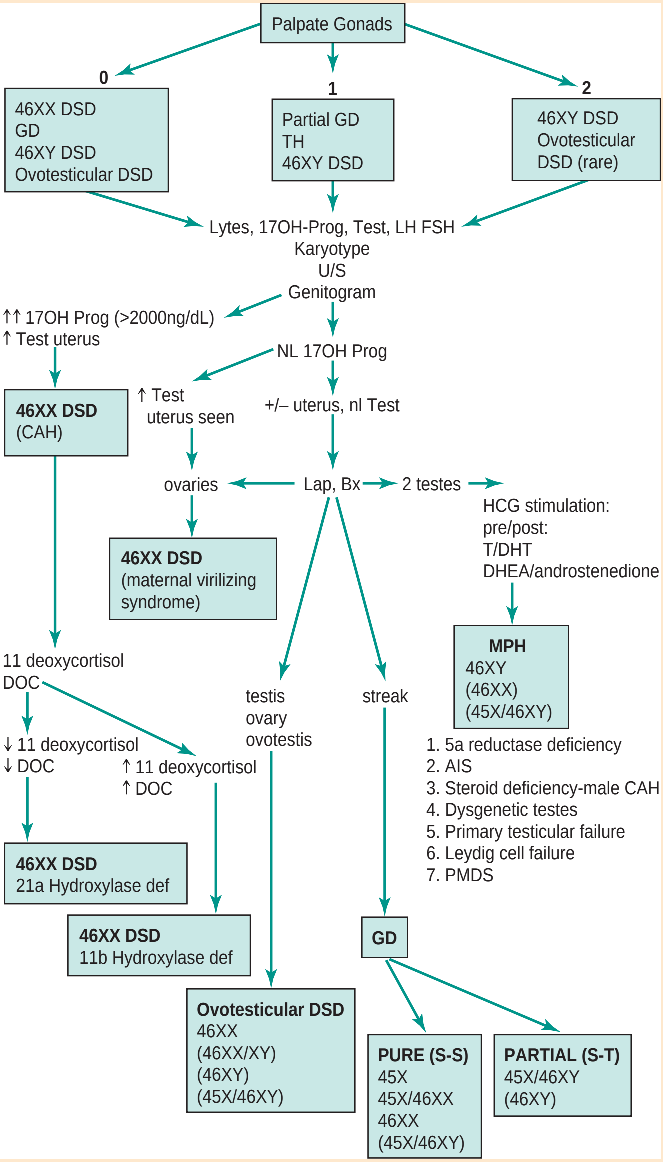


**Genetic Etiology of DSD**

| Syndrome | Karyotype | Genital Phenotype | Gene | Locus |
|---|---|---|---|---|
| 21-Hydroxylase | XX | virilized | CYP21B | 6p21.3 |
| deficiency | | | | |
| 11-Hydroxylase | XX | virilized | CYP11 (B1,B2) | 8q21-22 |
| deficiency | | | | |
| 3BHSD | XX | ambiguous | HSD3B2 | 1p13.1 |
| deficiency | XY | | | |
| 17a-Hydroxylase or | XX | ambiguous | CYP17 | 10q24-25 |
| 17,20 lyase | XY | | | |
| deficiency | | | | |
| 17BHSD | XY | ambiguous | 17BHSD3 | 9q22 |
| deficiency | | | | |
| Lipoid adrenal | XX | female, | StAR | 8p11.2 |
| hyperplasia | XY | ovarian failure (XX) | | |
| Leydig cell failure | XY | ambiguous | hCG/LH receptor | 2p21 |
| Androgen | XY | ambiguous | AR | Xq11-12 |
| insensitivity | | (female-AIS 7) | | |
| 5a-Reductase | XY | ambiguous, | SRD5A2 | 2p23 |
| deficiency | | pubertal virilization | | |
| Persistent | XY | male | AMH | 19q13.3 |
| müllerian duct | | | AMH II receptor | 12q13 |
| Gonadal dysgenesis: | | | | |
| complete | XX | female, | FSH receptor | 2p16-21 |
| | 45X, 45X/46XX | sexual infantilism | X monosomy | paternal X loss |
| | XY | | SRY | Yp53.3 |
| | | | DSS (DAX-1) | Xp 21-22 |
| | | | SOX9 | 17q24.3-25.1 |
| | | | WT-1 | 11p13 |
| Partial | 45X/46XY | ambiguous | unknown | unknown |
| | XY | | | |
| XY Dysgenesis | XY | ambiguous | SRY | Yp53.3 |
| | 45X/46XY | | DSS (DAX-1) | Xp 21-22 |
| | | | XH-2 | Xq13.3 |
| | | | WT-1 | 11p13 |
| | | | SOX9 | 17q24.3-25.1 |
| | | | SF-1 | 9q33 |
| Ovotesticular DSD | XX | ambiguous | SRY | Yp53.3 |
| | XX/XY | | testis cascade | unknown |
| | XY | | downstream genes | |
| Klinefelter | 47XXY | variable androgen | XY | sex chromosome |
| | 46XY/47XXY | deficiency | | nondisjunction |
| XX Testicular DSD | XX | ambiguous to | SRY | Y translocation to X |
| | | normal | | |

FIGURE 27.e1 Genetic characteristics of disorders of sex development (DSD).

## DIFFERENTIAL DIAGNOSIS



Decision pathway of evaluation for disorders of sex development (DSD)
T=testis, S=streak gonad

genital abnormalities. In contrast, HSD3B2, CYP17, and StAR deficiencies block cortisol synthesis and gonadal steroid production. Thus affected males have varying degrees of 46XY DSD (formerly male pseudohermaphroditism), whereas females generally have normal external genitalia. Each of these genetic defects is inherited in an autosomal recessive pattern.

## CYP21 (21A-HYDROXYLASE) DEFICIENCY

**Deficiency of** ***CYP21*** **(cytochrome p450$_{c21}$) is the most common cause of genital ambiguity.** The gene is located within the major human leukocyte antigen (HLA) locus on the short arm of chromosome 6 (6p21.3). HLA types are codominantly inherited and can be used as a marker to distinguish homozygous, heterozygous, and unaffected individuals.

Some centers have instituted screening for 17 hydroxyprogesterone levels at 3 to 5 days of life in conjunction with screening for other inborn metabolic diseases. HLA typing of amniotic fluid cells in mothers with a previously affected offspring has been used to identify a fetus with a *CYP21* deficiency. This has led to experimental prenatal treatment of CAH with good results of decreasing the masculinization. At issue is the controversy of initially treating one in eight fetuses who may not need the therapy.

## CYP11B1 (11β-HYDROXYLASE) DEFICIENCY

Cytochrome p450 is a terminal oxidase found on the inner mitochondrial membrane. Cortisol deficiency results in increased secretion of 11-deoxycortisol, DOC, corticosterone, and androgen by the adrenal gland. Hypertension, which occurs in about two thirds of patients, is presumptively a consequence of excess DOC, with resultant salt and water retention. Excess androgen secretion in utero masculinizes the external genitalia of the female fetus. After birth, untreated males and females progressively masculinize and experience rapid somatic growth and skeletal maturation.

Although *CYP11B1* and *CYP11B2* are extremely homologous, both genes are functional. Thus gene conversions are not the cause of impaired enzyme activity, as was described for 21α-hydroxylase deficiency. Similar to *CYP21,* alterations with less enzyme activity usually result in more severe phenotypes, but heterogeneity can occur. This disorder can be detected prenatally, and the masculinization of the fetus can be decreased following in utero dexamethasone treatment as previously described

Two *CYP21* genes are located on chromosome 6 between HLA-B and HLA-DR: a functional 10 exon *CYP21B* gene and a *CYP21A* pseudogene that are nonfunctional due to the presence of multiple stop codons. Recombination between *CYP21B* and the homologous but inactive *CYP21A* accounts for approximately 95% of 21α-hydroxylase deficiency mutations resulting in a variable decrease in 21α-hydroxylase activity. These conversions usually involve the transfer of inherent *CYP21A* mutations. Patients with simple virilizing 21α-hydroxylase deficiency have been noted to have a conversion mutation (Ile-Asn) causing severely decreased enzyme activity but sufficient aldosterone production to prevent salt wasting. Nonclassical CAH conversion mutations have been shown to display 20% to 50% of normal activity.

Two distinct enzymes, *CYP11B1* and *CYP11B2,* are encoded by two tandem and homologous genes at 8q21–22. *CYP11B1* encodes 11β-hydroxylase, which converts 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycortisol to cortisol. This gene's protein is expressed in the adrenal zona fasciculata and is primarily under the influence of corticotropin. Alternatively, *CYP11B2* encodes for aldosterone synthetase, which converts DOC to corticosterone and 18-hydroxycorticosterone to aldosterone. It is expressed in the zona glomerulosa and is under the influence of angiotensin II and potassium.

for 21α-hydroxylase deficiency. Other abnormalities such as 3*β*-hydroxysteroid dehydrogenase deficiency, CYP17 deficiency, and StAR deficiency are covered under disorders of 46XY DSD.

## 46XY DSD (Previously Called *Male Pseudohermaphroditism)*

**46XY DSD is a heterogenous disorder in which testicles are present but the internal ducts and/or the external genitalia are incompletely masculinized. The phenotype ranges from completely female external genitalia to mild male ambiguity (such as hypospadias or cryptorchidism).** 46XY DSD can result from eight basic etiologic categories:

1. Testicular unresponsiveness to human chorionic gonadotropin (hCG) and luteinizing hormone (LH) (Leydig cell aplasia/hypoplasia because of hCG/LH receptor defect)
2. Enzyme defects in testosterone (T) biosynthesis, some of which are common to CAH (StAR, HSD3B2, CYP17, 17-*β*HSD3)
3. Defects in androgen-dependent target tissues (androgen-insensitivity syndrome [AIS])
4. A defect in the enzymatic conversion of testosterone (T) to dihydrotestosterone (DHT) (5α-reductase deficiency)
5. Defects in the synthesis, secretion, or response to antimüllerian hormone (AMH) or müllerian inhibiting substance (MIS) resulting in persistent müllerian duct syndrome
6. Aberrations in testicular gonadogenesis (testicular dysgenesis)
7. Primary testicular failure (vanishing testes)
8. Exogenous insults (maternal ingestion of progesterone/estrogen or environmental hazards)

### LEYDIG CELL APLASIA/HYPOPLASIA

Leydig cell aplasia/hypoplasia is an autosomal recessive condition. In its complete form, these patients are 46XY but are cryptorchid and phenotypically female. Wolffian structures are present due to the secretion of MIS by intact Sertoli cells. However, the phenotypic presentation is variable. **The underlying abnormality in this disorder is a failure of Leydig cell differentiation secondary to an abnormal LH receptor (LHR). LH is elevated, T is markedly decreased, and follicle-stimulating hormone (FSH) levels are unaffected.** There is no T surge on hCG stimulation.

Different isoenzymes catalyze the isoreduction of estrone to estradiol and androstenedione to T.

## TESTOSTERONE BIOSYNTHESIS ENZYME DEFECTS

Defects in four steps of the steroid biosynthetic pathway from cholesterol to T may produce genital ambiguity in the male (Figure 27-1).

### StAR Deficiency

The StAR protein regulates the transfer of cholesterol from the outer mitochondrial membrane to the inner membrane, where it is metabolized by the *CYP11A* gene product, p450 scc.

These patients are often Asian and are born after an uneventful pregnancy. They subsequently present after a few days or weeks with severe adrenal insufficiency and will die from glucocorticoid and mineralocorticoid deficiency without hormone replacement. However, they can survive to adulthood if properly treated. 46XY males are born with female external genitalia, and the adrenal glands and testes are massively engorged with lipid deposits (cholesterol esters). Although 46XX females do experience feminization and cyclical vaginal bleeding at puberty, they invariably develop polycystic ovaries.

### 3β-Hydroxysteroid Dehydrogenase Deficiency

3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency results in impaired adrenal aldosterone and cortisol synthesis and gonadal T and estradiol formation. In its complete form, severe mineralocorticoid and glucocorticoid deficiency in the first week of life are observed. Male infants exhibit variable degrees of 46XY DSD, whereas in females, clitoromegaly and mild masculinization are common. The masculinization is a result of conversion of the Δ5 precursors to T via extragonadal (placenta and peripheral tissues) fetal 3β-HSD. Salt wasting may be present, depending on the severity of the 3*β*-HSD deficiency. Treatment involving glucocorticoids is similar to that of 21-hydroxylase deficiency, and mineralocorticoids are added to treat the salt wasting forms. Sex steroid replacement may be necessary at puberty.

### CYP17 Abnormality

The *CYP17* gene is located on chromosome 10q24.3 and contains eight exons. Its protein is absent from the placenta, ovarian glomerulosa cells, and the adrenal zona glomerulosa.

Congenital lipoid adrenal hyperplasia, a rare autosomal recessive disorder, was once thought to arise from mutations in the gene encoding p450 scc (cholesterol side chain cleavage), *CYP11A*. However, studies have shown that such mutations are incompatible with survival because these alterations would likely cause spontaneous abortions at the end of the first trimester from insufficient placental progesterone production, when corpus luteum secretion of progesterone wanes. Rather, lipoid CAH is a result of mutations in the *StAR* (steroidogenic acute regulatory) gene.

The cytochrome p450 c17 protein catalyzes 17α-hydroxylase and 17,20 lyase (desmolase) activities. Therefore mutations in *CYP17* would be expected to alter the activities of both enzymes. Although the existence of isolated 17,20 lyase deficiency has been questioned, two patients with hormonal and clinical findings consistent with isolated 17,20 lyase deficiency have been described.

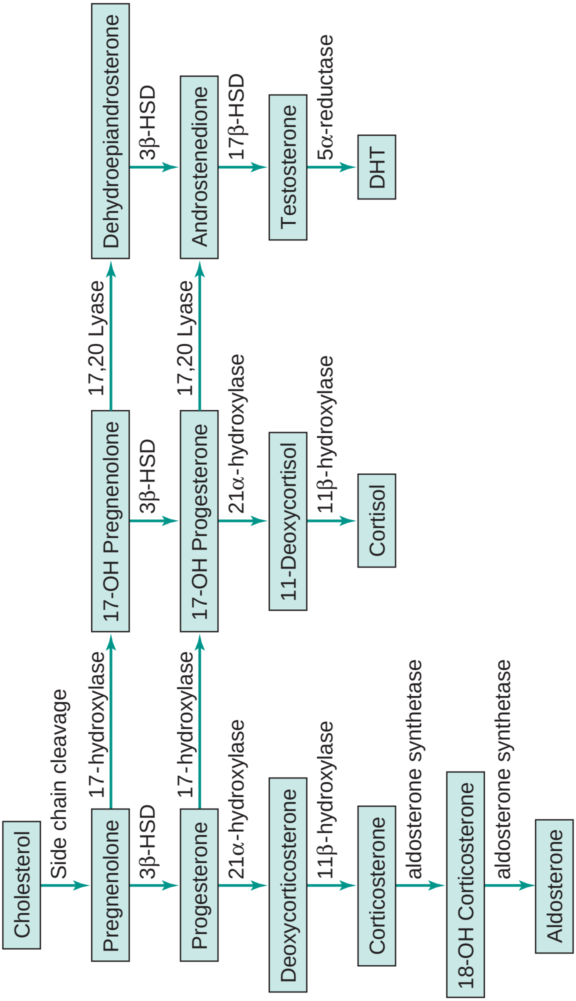


FIGURE 27-1 The disorders of sex development (DSD) steroid biosynthetic pathways with responsible enzymes.

Combined 17α-hydroxylase and 17,20 lyase deficiency causes deficient production of cortisol and sex hormones. Genetic females present with sexual infantilism due to a lack of ovarian estrogen synthesis at puberty, whereas genetic males often manifest a developmental spectrum ranging from a normal female phenotype to an ambiguous hypospadiac male. Overproduction of 11-DOC and corticosterone leads to hypertension, hypokalemic alkalosis, and carbohydrate intolerance. Genetic males with isolated 17,20 lyase deficiency also manifest variable degrees of incomplete masculinization. However, they do not suffer from the associated abnormalities in cortisol secretion and hypertension that occur in patients with combined 17α-hydroxylase and 17,20 lyase deficiencies.

## 17β-Hydroxysteroid Dehydrogenase Deficiency

There are at least five known isoenzymes of 17βHSD. The type 3 17βHSD catalyzes the reduction of androstenedione to T and is expressed only in the testis.

As expected, these patients have elevated plasma androstenedione (up to 10 times as high) levels, low plasma T (increased androstenedione-to-T ratio after hCG stimulation in prepubertal patients), elevated LH, and normal- to-high FSH levels. In these patients, more than 90% of plasma T is produced from the extragonadal conversion of androstenedione to T, compared to less than 1% in normal males. Plasma DHT may be normal in some patients, suggesting conversion from androstenedione.

These patients are usually 46XY males with ambiguous or female external genitalia and normal internal wolffian structures, including inguinal testes and a blind vaginal pouch. This occurs because there is little or no peripheral conversion of androstenedione to T and DHT during early gestation by the other 17βHSD isoenzymes. Additionally, increased aromatization of androstenedione to estrogen by the placenta may leave little substrate available for conversion to T and DHT. They are often raised as girls but may virilize at puberty and adopt a male gender role, similar to that seen in 5αRD-2 deficiency. At puberty, the expression of other 17βHSD isoenzymes in the peripheral tissues partially compensates for testicular 17βHSD-3 deficiency; however, the phenotype is variable. Some patients develop gynecomastia at puberty, depending on their T-to-estradiol ratio.

### 5α-Reductase Deficiency

**5α-reductase deficiency, an autosomal recessive condition with alterations of the 5αRD-2 gene, was initially described as pseudovaginal perineoscrotal hypospadias because of the striking genital ambiguity/female external phenotype** seen in these cases. These patients often have a clitorislike phallus, severely bifid scrotum, and perineoscrotal hypospadias. Some patients may have less severe genital ambiguity, however. Normal wolffian structures, cryptorchidism, and a rudimentary prostate are other common findings.

**At puberty, patients with 5α-reductase deficiency show signs of virilization with increased muscle mass, deepening of voice, substantial growth of phallus, rugation and hyperpigmentation of the scrotum, and normal libido.** Migration of inguinal testis into the scrotum has been observed. They do not experience gynecomastia or male pattern balding, facial hair is decreased, and their prostates remain infantile. Although these patients are usually oligo- or azoospermic, fertility via intrauterine insemination has been reported.

## ANDROGEN INSENSITIVITY SYNDROME

**The broad phenotypic spectrum in these 46XY patients varies from normal female external genitalia (AIS7 or testicular feminization—**Figures 27-2 **and** 27-3**) to normal males with infertility**

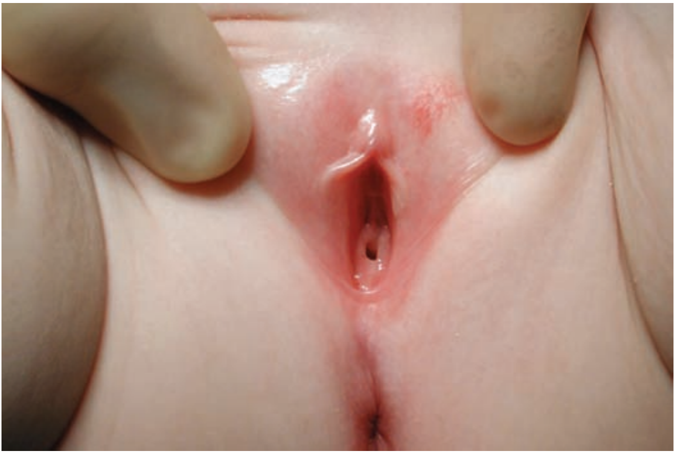


FIGURE 27-2 Normal introitus in 46XY patient with CAIS.

This X-linked disorder affects 1 in 20,000 live male births. The androgen receptor (AR) gene is located in the pericentromeric region of the long arm of chromosome X at Xq11-12 and contains eight exons. The AR is a member of the nuclear receptor superfamily of transcription factors and has three major functional domains. The amino ($NH_2$) terminal domain is encoded by exon 1 and is critical to target gene transcription regulation. Exons 2 and 3 encode the DNA-binding domain and the 5' region of exon 4 encodes the hinge region containing the nuclear targeting signal. The 3' region of exon 4 and exons 5 through 8 encode the steroid-binding domain that confers ligand specificity. Binding of DHT or T to this receptor ligand-binding domain results in "activation" of the receptor.

The $NH_2$ domain contains polymorphic glutamine (CAG) and glycine (GGC) repeats (i.e., the length of these repeats varies among individuals in the general population). Hence, AR genes with different CAG and GGC repeat lengths represent different AR alleles. Interestingly, AR CAG repeat length varies by racial group: the most common Caucasian AR allele has 21 repeats, whereas the most common black allele has 18 repeats. Deletion of the CAG repeat yields an AR with increased transcriptional activity, whereas an increase in the length decreases this activity. In men with spinal bulbar muscular atrophy and Kennedy disease, the AR CAG repeat is at least twice as long as that of unaffected men.

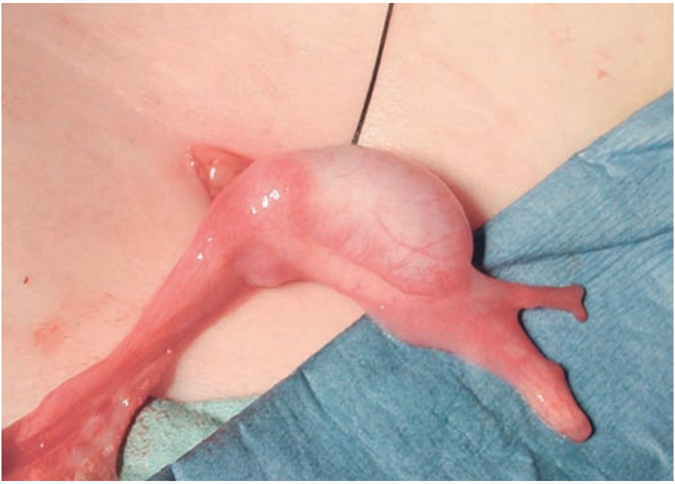


FIGURE 27-3 Abdominal testis identified at time of inguinal hernia repair in 46XY patient with CAIS.

**(AIS1). Patients previously described by Lubs, Gilbert-Dreyfuss, Reifenstein, and others are now classified as AIS 1-7.**

Mutations in the DNA-binding region can produce a receptor that binds androgen normally but cannot induce transactivation because of faulty binding to DNA, destabilization of the protein structure, or lack of dimerization of the receptor. The degree of impairment of transactivation correlates with the phenotype. The majority of AR gene mutations affects the steroid-binding domain and results in receptors unable to bind androgens or that bind androgens but exhibit qualitative abnormalities. Of note, however, is the finding of phenotypic variability in families with affected males with PAIS. This suggests that other factors in the sex-differentiation cascade influence the phenotypic manifestations of gene mutations.

## PERSISTENT MÜLLERIAN DUCT SYNDROME (HERNIA UTERI INGUINALE)

Persistent müllerian duct syndrome (PMDS) is a rare (autosomal recessive) disorder that arises from a **lack of MIS or AMH action on the müllerian ducts, resulting in the presence of müllerian structures in a normally masculinized XY male (Figure 27-4).**

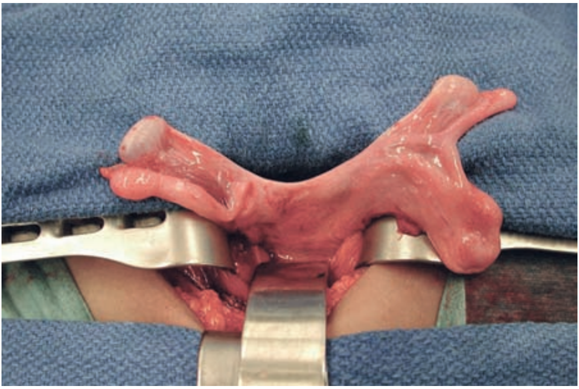


FIGURE 27-4 Retained müllerian structures in 46XY patient with persistent müllerian duct syndrome (PMDS).

**PMDS is due to either a mutation in the AMH gene or a defect in the AMH type II receptor.**

The diagnosis is often made at surgery for cryptorchidism or inguinal hernia repair. Patients with type I PMDS will have low or undetectable levels of serum MIS, whereas those with type II PMDS secondary to a defective AMH receptor will have high normal or elevated serum MIS levels. Treatment consists of orchidopexy. Historically, hysterectomy was recommended, but recent reports suggest that leaving the uterus and fallopian tubes in situ may be optimal to avoid injury to the vas deferens. The retained müllerian structures should not be at risk for malignant degeneration.

## 46XY GONADAL DYSGENESIS

Patients with dysgenetic gonads exhibit ambiguous development of the internal genital ducts, the urogenital sinus, and the external genitalia. Mutations or deletions of any of the genes involved in the testis determination cascade have been identified in dysgenetic MPH.

***SRY* is a single exon gene located on the short arm of the Y chromosome and is the "testis-determining factor." *SRY* gene mutations generally result in complete gonadal dysgenesis (CGD) and sex reversal.**

The AMH gene contains five exons and is located on chromosome 19p13.3. Alterations in the AMH gene were first reported in a Moroccan family and appear to occur mostly in Arab and Mediterranean countries, which have a high rate of consanguinity. They tend to be family specific and involve the entire length of the gene. The AMH receptor signals through two related but distinct receptors (type I and type II). The primary receptor (type II) binds MIS independently but requires the type I receptor for signal transduction. However, these mutations are not family specific and are more common in France and northern Europe, and the mutations in the AMH type II receptor are not as variable.

Histologic analysis of dysgenetic gonads of XY males revealed that those with normal *SRY* had some element of rete testis and tubular function, whereas those with *SRY* mutations had completely undifferentiated gonads similar to those of 45X individuals. Thus, *SRY* may have a direct role in testicular formation in addition to its indirect role in initiating the male differentiation cascade.

Duplication of the *DSS* (dosage-sensitive sex reversal) locus has been associated with 46XY gonadal dysgenesis (GD) and other anomalies. It has been mapped to the Xp21 region, which contains the *DAX1* gene. Mutations in *DAX1* can cause X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism. It is hypothesized that the duplicated gene escapes normal X inactivation, therefore disrupting testis formation despite *SRY* presence.

Male patients with Denys-Drash syndrome have ambiguous genitalia with streak or dysgenetic gonads, progressive neuropathy, and Wilms tumor. Analysis of these patients revealed heterozygous mutations of the Wilms tumor suppressor gene (WT1) at 11p13. Most *WT1* mutations in Denys-Drash syndrome occur de novo and act as dominant negative mutations.

The WAGR syndrome (Wilms tumor, aniridia, genitourinary [GU] abnormalities, mental retardation) is also associated with *WT1* alterations (heterozygous deletions). The GU anomalies in the WAGR syndrome are usually less severe than in Denys-Drash syndrome.

The *SOX9* gene (17q24.3-25.1) has been associated with campomelic dysplasia, an often lethal skeletal malformation, and 46XY GD. Affected 46XY males have phenotypic variability from normal males to normal females, depending on the function of the gonads. The *SOX9* protein is expressed in the developing gonad, rete testis, seminiferous tubules, and skeletal tissue.

## VANISHING TESTES SYNDROME

Vanishing testes syndrome (congenital anorchia) describes the spectrum of anomalies resulting from cessation of testicular function. **Loss of testes prior to 8 weeks gestation results in 46XY patients with female external and internal genitalia with agonadism or streak gonads. Loss at 8 to 10 weeks leads to ambiguous genitalia and variable ductal development. Loss of testis function after the critical male differentiation period (12 to 14 weeks) results in normal male phenotype externally and internally but anorchia.**

## SEX CHROMOSOME ANOMALIES

### 46XX Testicular DSD (Sex-Reversed Males)

About 1 in 20,000 phenotypic males have a 46XX karyotype. Categories include classic XX male individuals with apparently normal phenotypes, nonclassic XX males with some degree of sexual ambiguity, and XX ovotesticular DSD. Eighty percent to 90% of 46XX males result from an anomalous Y to X translocation involving the *SRY* gene during meiosis. The amount of DNA material involved in the exchange varies, but, in general, the greater the amount of Y DNA present, the more masculinized the phenotype.

# Gonadal Dysgenesis

GD disorders comprise a spectrum of anomalies ranging from complete absence of gonadal development to delayed gonadal failure. Complete (pure) GD includes failed gonadal development in genetic males and females as a result of abnormalities of sex or autosomal chromosomes. Partial gonadal dysgenesis (PGD) refers to disorders with partial testicular formation at some point in development including partial GD, 46XY GD, and some forms of testicular regression.

## COMPLETE GONADAL DYSGENESIS

**The bipotential gonad differentiates into an ovary if testicular formation fails. However, if one X chromosome is present, the gonad develops into an ovary but then degenerates into a streak gonad with ovarianlike stroma and little or no germ cells.**

XY GD (XY sex reversal or Swyer syndrome) occurs secondary to the absence of testes despite a Y chromosome. These patients appear female externally with internal müllerian ducts and bilateral streak gonads. They also display sexual infantilism at puberty. It is a heterogenous condition that can result from deletions of the short arm of the Y chromosome, SRY gene mutations, alterations in autosomal genes, or duplications of the DSS locus on the X chromosome. Other genetic alterations that may cause this type of GD (WT1, DAX1, SOX9) have been previously discussed in the section on XY GD.

Noonan syndrome patients (often referred to as *male Turner syndrome*) display Turner-like stigmata including short stature, webbed neck, and right heart disease. They have a normal sex chromosome constitution often with cryptorchidism of hypoplastic testes. Puberty is delayed and androgen deficiency can be seen. However, fertility may occur in the absence of cryptorchidism. Most cases are sporadic, but familial clusters are consistent with an autosomal dominant inheritance.

46XX pure GD is characterized by normal stature, normal external and internal female genitalia, sexual infantilism, and bilateral streak gonads. It is a heterogenous condition occurring sporadically or, when familial, as an autosomal recessive trait.

**The cardinal features of 45X GD (Turner syndrome) includes webbed neck, shield chest, short stature, cardiac anomalies** (**coarctation of the aorta**)**, and sexual infantilism.** Although bilateral streak gonads are the rule, primary follicles have been described in the genital ridges of some 45X individuals correlating with the rare occurrence of menarche. Conceptions have been documented despite karyotyping revealing only 45X cell lines. A 45X constitution may be due to nondisjunction or chromosome loss during gametogenesis in either parent resulting in a sperm or ovum without a sex chromosome. 45X/46XX mosaicism may be present in up to 75% of Turner syndrome patients.

### PARTIAL GONADAL DYSGENESIS

PGD is a result of impaired testicular determination in the presence of SRY resulting in PGD. The phenotypes vary, including bilateral testicular dysgenesis (46XY GD), a testis and a streak gonad (partial or mixed GD), and absence of one or both testes (testicular regression). The majority of PGD patients have a 45X/46XY karyotype, but 46XY is also seen. In contrast to patients presenting with genital ambiguity and mosaicism, 95% of prenatally detected 45X/46XY mosaics have a normal male phenotype. This contradiction may be related to separate cell lines in the streak gonad and the testis. Mutations in the pseudoautosomal region of the Y chromosome upstream of the *SRY* gene have been identified in PGD. Many of the previously discussed mutations associated with CGD (WT1, DAX1, 10qdel) have also been reported in PGD, although the etiology of GD remains unknown in most cases.

## Ovotesticular DSD (Previously Called *True Hermaphroditism*)

**Ovotesticular DSD**, previously referred to as *true hermaphroditism*, **requires the presence of both ovarian and testicular tissue in the individual.** This uncommon condition may be classified into three groups:

1. Lateral: testis and ovary (usually left)
2. Bilateral: ovotestis and ovotestis
3. Unilateral (most common): ovotestis and testis or ovary

The genital development is ambiguous with hypospadias, cryptorchidism, and incomplete fusion of labioscrotal folds. Genital duct differentiation generally follows that of the ipsilateral gonad.

Ovotesticular DSD can result from sex chromosome mosaicism, chimerism, or Y chromosomal translocation. The most common karyotype is 46XX, followed by 46XX/46XY chimerism/mosaicism and 46XY. Most 46XX ovotesticular DSD patients are *SRY*-negative, and the genes responsible have not yet been identified. A mutated downstream gene in the sex-determination cascade likely allows for testicular determination.

Although sex chromosome mosaicism arises from mitotic or meiotic errors, 46XX/46XY chimerism is usually a result of double fertilization (an X sperm and a Y sperm) or, less commonly, fusion of two normally fertilized ova. Thus chimeric patients have two distinct cell populations. The least common form of ovotesticular DSD, 46XY, may result from a cryptic 46XX cell line or gonadal mosaicism with a mutated sex-determination gene.

### CLINICAL PEARLS

- 46XX DSD (CAH) is the most common DSD disorder.
- Gonadal dysgenesis (GD) disorders comprise a spectrum of anomalies ranging from complete absence of gonadal development to delayed gonadal failure.
- 46XY DSD is a heterogenous disorder in which testes are present but the internal ducts and/or the external genitalia are incompletely masculinized.
- Ovotesticular DSD requires the presence of both ovarian and testicular tissue in the individual and can result from sex chromosome mosaicism, chimerism, or Y chromosomal translocation.

## History and Physical Exam

Patient history should include the level of prematurity, ingestion of exogenous maternal hormones such as those used in assisted reproductive techniques, and maternal use of oral contraceptives during pregnancy. A family history is also useful for any urologic abnormalities, neonatal deaths, precocious puberty, infertility, or consanguinity. Any abnormal masculinization or cushingoid appearance of the child's mother should also be noted. Abnormalities of the prenatal maternal ultrasound are also helpful, such as discordance of the fetal karyotype with the genitalia by sonogram (Figure 27-5).

On physical examination, one should note any dysmorphic features including a short, broad neck or widely spaced nipples. The patient should be examined in a warm room supine in the frog leg position with both legs free. An abnormal phallic size should be documented by width and stretched length measurements. I prefer to

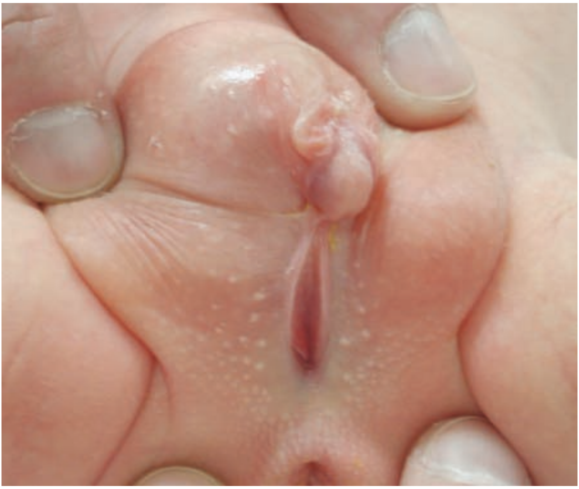


FIGURE 27-5 46XY patient with severe hypospadias and bilateral cryptorchidism because of 46XY testicular dysgenesis.

measure the penis by grasping the glans with a gauze pad, pressing down on the penopubic angle with a cotton tip applicator, and stretching the penis against the applicator to measure. One should describe the position of the urethral meatus and the amount of chordee (ventral curvature) and note the number of orifices: three in girls (urethra, vagina, and anus) or two in boys (urethra, anus). A rectal exam with your fifth finger should also be performed for palpation of a uterus. With warmed hands, one should begin the inguinal examination at the anterior superior iliac crest and sweep the groin from lateral to medial with a nondominant hand. Once a gonad is palpated, grasp it with the dominant hand and continue to sweep toward the scrotum with the other hand to attempt to bring the gonad to the scrotum. Occasionally, some soap or lubricant on the fingertips may aid in this examination. It is important to check size, location, and texture of both gonads if palpable. The undescended testis may be found in the inguinal canal; in the superficial inguinal pouch; at the upper scrotum; or rarely in the femoral, perineal, or contralateral scrotal regions. Also note the development and pigmentation of the labioscrotal folds along with any other congenital anomalies of other body systems.

**For differential diagnosis and treatment purposes, the distinction needs to be made whether or not the gonad is palpable** (see Differential Diagnosis, Page 2). Unless associated with a patent processus vaginalis, ovaries and streak gonads do not descend, whereas testes and rarely an ovotestis may be palpable. If no gonads are palpable, any DSD diagnosis is possible. Of these, 46XX CAH is most commonly seen, followed by MGD. If one gonad is palpable, 46XX DSD (CAH) and PGD are ruled out, whereas MGD, ovotesticular DSD, and 46XY DSD remain possibilities. If two gonads are palpable, 46XY DSD and rarely ovotesticular DSD are the most likely diagnoses. In 46XY boys, hypospadias and cryptorchidism without an underlying DSD etiology would be diagnoses of exclusion after a full evaluation.

## Patient Evaluation

**All patients require laboratory evaluation by karyotype, serum electrolytes, 17OH-progesterone, T, LH, and FSH levels.** If the 17OH-progesterone level is elevated, 11-deoxycortisol and DOC levels will help differentiate 21α-hydroxylase deficiency from 11ß-hydroxylase deficiency. If the 17OH-progesterone level is normal, a T-to-DHT ratio, along with androgen precursors before and after hCG stimulation, will help elucidate the 46XY DSD etiology. During the period of 60 to 90 days of life, there is a normal gonadotropic surge with a resultant increase in the T level of the infant. During this specific time period, one can forego the hCG stimulation for the androgen evaluation. A failure to respond to hCG in combination with elevated LH and FSH levels is consistent with anorchia.

**An ultrasound can identify a müllerian structure or gonads in the inguinal region where they are also most easily palpable, but it is only 50% accurate in showing intraabdominal testes (and should never be used solely for this purpose).** A genitogram will evaluate a urogenital sinus including the entry of the urethra in the vagina along with a cervical impression. A magnetic resonance imaging scan with gadolinium may also better delineate the anatomy, although it more expensive and requires general anesthesia. DSD infants, other than CAH, often require an open or laparoscopic exploration with bilateral deep longitudinal gonadal biopsies for histologic evaluation.

**CLINICAL PEARLS**

- A newborn boy with bilateral nonpalpable testes must be evaluated for disorders of sex development (DSD) and should not be circumcised until after the workup is complete.
- If no gonads are palpable, all DSD diagnoses are possible.
- If one gonad is palpable, 46XX DSD and PGD are ruled out because ovaries and streak gonads do not descend. MGD, ovotesticular, and 46XY DSD remain possibilities.
- If two gonads are palpable, 46 XY DSD and (rarely) ovotesticular DSD are the most likely diagnoses.

## Treatment Options and Indications

Much current research is aimed at understanding the influence of androgens on the fetal and newborn brain and its relationship to gender identity. Diagnosis and management of these children are very individualized and should always involve a team approach, which includes the pediatric urologist, endocrinologist, geneticist, psychologist, and the child's parents immediately after birth.

### 46XX DSD (CAH)

**Treatment of the newborn with CAH involves the correction of dehydration and salt loss by electrolyte and fluid therapy with mineralocorticoid replacement. Glucocorticoid replacement is then generally added on confirmation of the diagnosis.** Infants who are going to be raised as girls usually undergo clitoral reduction and vulvovaginoplasty in early infancy, but **controversy exists on the timing of surgery, and all aspects must be weighed prior to decision making.** Surgery can be performed on an infant, toddler, or adolescent. Many surgeons advocate early surgery for both technical and psychologic reasons, realizing that vaginal revision may be needed after puberty. Surgery has three main aims: reducing the size of the enlarged masculinized clitoris, reconstructing the female labia, and increasing the opening and possibly length of the vagina. These procedures have gone through many changes during the history of surgery. Surgical technique continues to be revised to optimize the girl's external appearance and functional size while maintaining adequate sensation. Clitorectomy, which involves removing the entire clitoris, is long out of practice as is clitoral recession without reduction because it is associated with painful erections on stimulation. Reduction clitoroplasty is the operation of choice for most infants with severe clitoromegaly. The central portions of the corporal bodies are excised, and the surgeon preserves the dorsal neurovascular bundles by incising the Buck fascia laterally at the 3-o'clock and 9-o'clock positions. The corporal bodies need to be dissected beyond the bifurcation to the inferior pubic rami where they are transected. The remaining proximal and distal portions of the bodies are then reapproximated and placed in the investing fascia. This optimizes future erectile function and sensation. A glansplasty is rarely required for an extremely large glans. A vulvoplasty is carried out by extending the incision for the clitoroplasty on either side of the midline strip of tissue down to the level of the vaginal orifice. Redundant labial scrotal skin is brought down as preputial flaps to form the labia minora.

The position of the vagina should be accurately determined preoperatively by the genitogram as part of the workup for DSD. There are four main types of vaginal repair: a simple "cutback" of the perineum, a "flap" vaginoplasty, a "pull-through" vaginoplasty, or a more extensive rotation of skin flaps or segmental bowel interposition. Usually a low vaginoplasty can be performed at the same time as the clitoroplasty. When the vagina opens very low, a simple cutback with a vertical midline incision may be all that is needed to open the introitus. Usually, however, a posterior based U-shaped flap is necessary for a tension-free anastomosis, reducing the risks of postoperative vaginal stenosis. Exposure of the high vagina requires either a perineal approach, a posterior vaginoplasty, or an anterior sagittal transanorectal vaginoplasty. When the vagina is extremely high and small, replacement with a bowel segment will be necessary, usually with the sigmoid colon.

## GONADAL DYSGENESIS

A streak gonad does not descend, but it may be palpable as a small remnant of tissue in an inguinal hernia sac. If a dysgenetic testis is in the inguinal position, it can be removed using an incision in the groin as for a traditional orchiopexy or hernia repair. If the gonad is in the abdomen as is usually the case with the GD, then the treatment options include open abdominal exploration and removal of the gonads or laparoscopic gonadectomy, which is the usual preference. When a purely female anatomy exists, such as in Turner syndrome or Swyer syndrome, no treatment may be necessary. These girls have sexual infantilism at puberty marked by no onset of secondary sexual development. Some degree of female development, however, may be seen in up to 20% to 25%. **Because gonadoblastoma can occur in the presence of Y chromosome material, removal of the streak gonads is required in these cases.** Growth hormone is usually recommended early in childhood, and estrogen therapy is begun after puberty to optimize the patient's height. Although rare cases of spontaneous pregnancy have been reported, infertility usually occurs. Pregnancy may be possible using donor eggs and assisted reproductive techniques.

## OVOTESTICULAR DSD

Generally, a female sex has been assigned to most patients because of the presence of a vagina, uterus, and ovarian tissue. Less commonly, the patient has a 46XY karyotype with adequate penile development and without a uterus present, so a male sex assignment would be more appropriate. The decision of sex of rearing should always be deferred until the child has had an adequate evaluation of the GU system. **Usually, the internal organs need to be visualized and the gonads biopsied. This can be done through an open abdominal exploration or accomplished with the use of the laparoscope.** If raised as a female, the child should have dysgenetic testicular tissue removed because of the risk of malignancy. The possible need for vaginoplasty can be performed early or deferred until puberty. If the child is raised as a boy, he should have any hypospadias or cryptorchidism repaired as an infant. T supplementation may be needed if the amount of testicular tissue present is inadequate to begin or continue puberty. A persistent müllerian duct, such as a uterus and fallopian tubes, has usually not fully regressed and connects to the urethra near the bladder at the verumontanum. If there is a decision to rear the child as a boy, the structures are generally removed, taking care not to injure the vas deferens which usually runs along side the uterus. Extensive dissection behind the bladder neck and up to the area where the müllerian structures insert into the urethra is usually contraindicated to avoid damage to the sphincter mechanism risking incontinence. Both open and laparoscopic excisions have been reported. Arguments for removal of the müllerian structures include the possibility of cyclic hematuria postpuberty or the formation of stones or chronic urinary tract infections if the continuity with the urethra is maintained and stasis occurs in a dilated müllerian remnant. Arguments against removal maintain that complications from the structures are uncommon and their removal risks injury to the vas deferens, the bladder neck, and the urethral sphincter.

## 46XY DSD

Decreased masculinization (hypospadias with cryptorchidism or more ambiguous development) is seen in most patients with XY DSD. In untreated patients with 5α-reductase deficiency, significant virilization occurs at puberty as T levels increase into the adult male range, whereas DHT remains disproportionately low. Treatment is currently unclear for this enzyme deficiency when diagnosed in infancy. Male gender assignment has been recommended because the natural history of this deficiency is virilization at puberty with subsequent change to male gender. However, this decision requires surgical hypospadias repair and orchiopexy with male hormonal replacement.

Rarely do patients with dysgenetic testes have fully masculinized external genitalia. The surgical issues are very dependent on the degree of virilization in each individual case. This will also influence the decision process of sex assignment. If a 46XY infant with testicular dysgenesis is going to be raised as a male, he will need a hypospadias repair, orchiopexy, or possibly orchiectomy. Müllerian ducts have usually not fully regressed and may be fully or partially removed at the time of other repairs to facilitate orchiopexies. As previously discussed, retained female structures have the potential for urinary tract infections, stones, or even cyclic hematuria at puberty. **Dysgenetic testes may appear normal grossly but microscopically are disorganized and poorly formed; thus a biopsy of the gonad is recommended in most children undergoing DSD evaluation. Currently, the recommendation is to remove an undescended dysgenetic testis because of the risk of malignancy. In 45X/46XY patients, if the biopsy is normal and the testis is scrotal or can be placed in the scrotum, it should not be removed, but a risk of malignancy correlates with the extent of testicular decent.** Tumors have also been reported in scrotal dysgenetic testes. A scrotal testis needs to be followed very closely for this reason. The possibility does exists of a male gender in these patients who would require a hypospadias repair yet would have removal of severely dysgenetic testis requiring replacement hormones. It would seem obvious that treatment in these cases needs to be individualized. The child's parents should discuss with the pediatric urologist, endocrinologist, geneticist, and psychiatrist the issues of T imprinting in utero, the need for hormones prepuberty and postpuberty, the degree of masculinization, the function of the testis, and the extent of surgery that is required.

Affected boys with errors in T production are undermasculinized with varied degrees of hypospadias, cryptorchidism, bifid scrotum, or a blind vaginal pouch. For the patient reared as a boy, T therapy may be indicated to augment penile size and to aid in the hypospadias repair. Some enzyme deficiencies require glucocorticoid and mineralocorticoid replacement, and all of these patients need T replacement at puberty for masculinization. Gonadectomy is required in 46XY patients raised as girls to address the risk of tumor formation in the future.

Traditionally, a child with complete androgen-sensitivity syndrome would be raised as a girl. Most of these children are not diagnosed until a workup is performed when amenorrhea occurs at puberty. Occasionally, it is discovered at the time of inguinal hernia repair or when a prenatal karyotype does not match the external phenotype of the newborn child. If the child is to be raised female, an orchiectomy is recommended for future cancer risk. **The testes are at risk for cancer development and the incidence of malignant tumors is estimated to be 5% to 10%. Seminoma is the most common tumor seen, but nonseminomatous germ cell tumors and other malignancies have also been reported**. Tumor risks appear to be greater in older patients and in those with partial rather than complete androgen insensitivity; tumor formation appears to occur after puberty. Intratubular germ cell neoplasia has been identified in prepubertal boys with partial AIS but not complete AIS. Vaginal dilation or vaginal augmentation may or may not be needed. This usually is reserved until after puberty and a number of techniques are available. In patients with partial AIS, orchiectomy is recommended as soon as the diagnosis is made to avoid further virilization in patients who will be raised in the female gender. Male gender assignment is usually successful in patients with a predominantly male phenotype; however, predicting the adequacy of masculinization in adulthood may not be possible based on the maternal family history or characterization of the AR genetic defect. Some children respond well to high-dose androgen therapy, but its durability is not yet clear.

**The timing of gonadectomy is controversial (prepuberty versus postpuberty), and endocrine, oncologic and psychological issues**

**are taken into account. The incidence of malignancy associated with CAIS is about 0.8% and usually occurs after puberty, though there have been a case report of a malignant abdominal yolk sac tumor in a 17-month-old child, uncommon carcinoma in situ, and several reports of benign abdominal masses. The incidence of tumor formation in PAIS is much higher, and early gonadectomy is recommended unless the testis can be brought into the scrotum and adequately monitored.** In an infant with complete AIS, some advocate that the testes should be left in place until after puberty to take advantage of the endogenous hormonal function, and in this way, natural female pubertal changes can occur by T conversion to estrogen, which can then be augmented by exogenous estrogen. These purported advantages, though, have not been documented in a scientific study. After puberty is completed, the testes would be removed and replacement estrogen continued. Other risks to be discussed include: inguinal testes are easily injured; psychologic issues, including explaining to a mature postpubertal patient of the need to remove her testes; the risk of testis cancer increases if the patient is lost to follow-up care; and early orchiectomy requires full replacement hormones for pubertal changes.

## GENDER ASSIGNMENT

Gender assignment in the patient with DSD can often be a difficult decision, with two differing viewpoints regarding the timing of gender assignment. The first is to assign and complete genital reconstruction shortly after birth, which may avoid internal conflicts with the patient or external societal conflicts as the child develops. Opponents argue that gender reassignment should be a decision of the affected individual during puberty. They maintain that neither the physician nor the family can predict future gender identity and sexual orientation for the individual. Nevertheless, **the decision regarding assignment of sex for rearing should be guided by three equally important factors: the functional and anatomic abilities of the genitalia (i.e., phallus/vagina size, fertility potential), cause of the DSD condition, and family values and desires.**

**One factor in the decision-making process that is becoming clearer is the large body of evidence to support the notion that the prenatal and postnatal hormonal milieu has an important role in predicting gender and sexual identity.** For instance, genetically female rats given testosterone shortly after birth do not exhibit typical female behavior during adulthood. One study showed that among CAH girls with excessive prenatal androgen exposure, many have tomboyish personalities and are more likely to have bisexual or homosexual interests than women without CAH. Among women affected by CAH from 21-OH deficiencies, there appears to be outcome differences between the more severe salt-losing form and simple virilizing forms. Women with simple masculinizing CAH (when the deficiency is partial) reported greater satisfaction and fewer concerns with regard to their psychosexual outcomes compared to women with the more severe salt-losing form.

In general, newborns with ambiguous genitalia from CAH have normal ovaries and uterus and should be raised as females. In cases of bilateral testicular dysgenesis where a vagina and uterus are present, female assignment may be desirable. Likewise, in cases of complete androgen-insensitivity syndrome, a female orientation is correct. For most other instances of partial resistance, it is desirable to opt for male rearing. Male rearing is also appropriate when a deficit in 5α-reductase is identified because further virilization occurs during puberty. In cases where ovarian function may be preserved, female assignment is preferable for these cases of ovotesticular DSD. When a decision for female rearing is made in 46XY DSD, removal of testicular tissue is performed. If raised as males, these patients require careful follow-up because of the increased risk of gonadal tumors.

## CLINICAL PEARLS

- Treatment of the newborn with congenital adrenal hyperplasia (CAH) involves correction of dehydration and salt loss by electrolyte and fluid therapy with mineralocorticoid replacement. Glucocorticoid replacement is generally added on confirmation of the diagnosis.
- Estrogen replacement is begun after puberty in girls with complete androgen-insensitivity syndrome (AIS). Testosterone replacement may be needed in some cases of XY DSD (partial AIS, testicular dysgenesis, primary testicular, or Leydig cell failure) to aid in pubertal changes and for maintenance through adulthood.
- Some gonads need to be removed because of the risk of tumor formation, especially in girls with a Y chromosome.

## FOLLOW-UP

**Treatment of the child with DSD should not end with the first postoperative visit.** A boy should be evaluated 6 to 12 months after orchiopexy for testes size, location, and viability. The parents should be made aware of the issues regarding cancer and infertility. Starting at puberty, the boy should be shown how to perform monthly testicular self-exams and offered a semen analysis check at age 18. Orchiopexy is not protective against testis cancer development, but it does allow easier palpation for subsequent physical exams. Although intraabdominal testes comprise only 10% to 15% of all undescended testes, they account for almost 50% of those testes that develop cancer. The most common tumor in an undescended testes is a seminoma. Up to 35% of dysgenetic testes may develop cancer, most commonly a benign tumor called *gonadoblastoma*. Although this tumor does not spread, it can develop into a malignant form called a *dysgerminoma*. Patients with a 45X/45XY mosaic karyotype also have an increased risk of CIS. Some surgeons have recommended ultrasound and biopsy of a testis at puberty. Ultrasound is then performed yearly until age 20 when a repeat biopsy is performed. Absence of CIS at age 20 suggests that the risk of CIS is minimal.

The patient with hypospadias repaired as a child should remain in follow-up with his physician to identify and correct any long-term complications of the surgery. It is also important to document adequate control of voiding and the force of urinary stream. There appears to be no increase in infertility from a purely urethral point of view rather than that previously described for cryptorchidism.

Cosmetic and functional results improve yearly with advances in optical magnification, instrumentation and sutures, and tissue handling. Continuous research in this area allows the surgeon to refine the technique and provide the patient with the best repair possible. Girls who have undergone a feminizing genitoplasty require long-term follow-up for issues of menstruation, intercourse, and sensation as previously described. With a proper assignment of sex of rearing and a continued management with continuity of care, DSD individuals should be able to lead well-adjusted lives and ultimately obtain sexual satisfaction. Simple yet comprehensive discussions with all physicians involved and the parents must take into account parental anxieties and social, cultural, and religious views to obtain appropriate gender assignment.

New molecular biology techniques have allowed genetic analysis to be commonplace for patient evaluation. As new genes have been described, a complex yet specific pathway of sex determination and development has evolved that allows us to formulate clinical algorithms for both prenatal and postnatal diagnosis and treatment. The future holds great promise for the further definition of the genes involved in urogenital development and function.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *The physical characteristic most useful in the initial evaluation of the child with disorders of sex development (DSD) is:*
    *A. Position of the urethral meatus*
    *B. Length of the phallus*
    *C. Presence of a müllerian structure*
    *D. Palpable gonads*
    *E. Labioscrotal rugae*
2. *The enzyme deficiency that does not undermasculinize a 46XY boy is:*
    *A. 17 hydroxylase*
    *B. 17,20 lyase*
    *C. 17 hydroxysteroid dehydrogenase*
    *D. 3B HSD*
    *E. 21 hydroxylase*
3. *The phenotype not seen in androgen-insensitivity syndrome is:*
    *A. Distal hypospadias*
    *B. Proximal hypospadias*
    *C. Unilateral cryptorchidiam*
    *D. Infertility*
    *E. Streak gonad*
4. *The DSD diagnosis at highest risk for gonadal tumor is:*
    *A. Complete androgen-insensitivity syndrome (AIS)*
    *B. Congenital adrenal hyperplasia (CAH)*
    *C. 45X/46XY mixed gonadal dysgenesis (GD)*
    *D. Ovotesticular syndrome*
    *E. 5-α reductase deficiency*
5. *Gonadectomy is recommended for all of the following diagnoses except:*
    *A. 45X Turner syndrome*
    *B. Frasier syndrome*
    *C. PAIS nonscrotal*
    *D. 46XY Denys-Drash syndrome*
    *E. 45X/46XY pure GD*

6. *The laboratory test(s) most helpful in identifying 46XY 5-α reductase deficiency is:*
   - *A. 17-OH pregnenolone*
   - *B. 11-deoxycortisol*
   - *C. DHEA: androstenedione ratio*
   - *D. Testosterone: DHT ratio*
   - *E. 17-OH progesterone:androstenedione ratio*

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# CHAPTER 28

# Pediatric Oncology

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## Wilms Tumor

### GENERAL

1. Characterized by Wilms in 1899 and first described by Rance in 1814
2. Seven new cases per 1 million children per year in North America (450 cases per year)
   a. Eighty percent of all childhood solid tumors
   b. Eighty percent of all genitourinary (GU) cancers in children younger than 15 years
   c. Seventy-five percent in children between 1 and 5 years of age; peak incidence 3 to 4 years of age, 90% before 7 years of age
   d. Male-to-female ratio equal, 1% familial, slightly higher rates in black population and lower in Asian children

### PATHOLOGY — EMBRYOLOGY

1. Gross pathologic features
   a. Sharply demarcated, encapsulated
   b. Usually solitary
   c. Frequently hemorrhagic or necrotic
   d. True cyst formation rare
   e. Pelvis invasion rare, venous invasion 20%
   f. Extrarenal sites (retroperitoneum, inguinal, mediastinal, sacrococcygeal) rare
2. Microscopic features — wide spectrum
   a. Triphasic: Metanephric blastema, epithelium (glomerulotubular), and stroma (myxoid, occasionally differentiated into striated muscle, cartilage, or fat)
   b. Unfavorable histology (UH) in 10% of cases; two types:
      1) Anaplasia: Threefold variation in nuclear size with hyperchromism and mitoses; monomorphic sarcomatous-appearing tumors

        2) Rhabdoid: Uniform large cells with large nuclei, prominent nucleoli, and eosinophilic cytoplasmic inclusions (fibrils), metastasizes to brain, is probably not metanephric. Rhabdoid tumor of the kidney and clear-cell sarcoma of the kidney have been reclassified and are now considered distinct entities from Wilms tumor sarcoma.
        3) Clear cell sarcoma, "bone metastasizing tumors of childhood": Vasocentric spindle cell pattern, may be malignant version of congenital mesoblastic nephroma (pure blastemal origin) and not a true form of Wilms tumor
    c. Favorable histology (FH) consists of all other types, tubular predominance perhaps being most favorable of all.
    d. Cystic nephroma (CN) and cystic, partially differentiated nephroblastoma (CPDN) are benign neoplasms currently considered by many experts to be part of the spectrum of nephroblastoma; tumors occur in both adults and children and are generally asymptomatic but may cause hematuria. CNs are all cystic, without solid component, with septa purely stromal without blastemal elements. CPDN is also cystic, but septae contain blastemal elements (or nephrogenic rests). It is important to note that nephroblastomas, clear-cell sarcomas, and mesoblastic nephromas may also be predominantly cystic.
    e. Congenital mesoblastic nephroma occurs in early infancy. It is associated with polyhydramnios, resembles leiomyoma grossly, and histologically exhibits sheets of spindle-shape uniform cells that appear to be fibroblasts. There is no capsule but when completely excised, it follows a benign course; it may be a hamartoma. The spindle-cell variant may behave with a more malignant potential.
3. Genetics and associated anomalies
    a. 11p chromosomal deletion and sporadic, not congenital, aniridia associated with a 20% incidence of Wilms tumors
    b. 11p deletion common in tumor genotype, 12q also reported
    c. Trisomy 8 and 18, 45 XO (Turner), and XX/XY mosaicism associated
    d. Loss of heterozygosity for portion of chromosome 16q may portend poorer outcome.

   e. Sporadic (nonfamilial) aniridia associated; full syndrome includes early tumor (less than 3 years) and other GU anomalies; external ear deformities, retardation, facial dysmorphism, hernias, and hypotonia.
   f. Hemihypertrophy (1 in 14,000 general population, 1 in 32 in Wilms patients) along with other malignancies (i.e., adrenal carcinoma, hepatoblastoma), and pigmented nevi and hemangiomas
   g. Beckwith-Wiedemann syndrome: Visceromegaly involving adrenal, kidney, liver, pancreas, often with hypoglycemia; gonads with omphalocele, hemihypertrophy, microcephaly, retardation, macroglossia; 10% develop a neoplasm of liver, adrenal, or kidney.
   h. Musculoskeletal deformities exhibited in 2.9% with 30-fold increase in neurofibromatosis incidence.
   i. GU anomalies exhibited in 4.4%, including renal hypoplasia, ectopia or fusion, duplications, cystic disease, hypospadias, cryptorchidism, and pseudohermaphroditism.
4. The nephroblastomatosis complex appears to be a precursor of Wilms tumor and consists of persistent primitive metanephric elements beyond 36 weeks of gestation; it occurs in three forms.
   a. Superficial infantile form in which the entire kidney is replaced by blastema; infant presents with massive nephromegaly and dies shortly after birth; rarest form.
   b. Multifocal juvenile form or nodular renal blastema (NRB) consists of gross or microscopic NRB nodules that may be sclerotic or glomerulocystic and papillary, usually in the subcapsular region or along the columns of Bertin.
   c. Wilms tumorlet exhibits triphasic histology and nodules between 1 and 3.5 cm.
   d. Some component of nephroblastomatosis is present in 100% of bilateral Wilms patients and in at least 40% of unilateral cases.
   e. May represent Wilms tumor precursor in the “two-hit” theory of oncogenesis of Knudson and Strong
   f. NRB should be sought, mobilizing and inspecting the contralateral kidney carefully. Any area of abnormal color or a cleft should be biopsied; it does respond to chemotherapy, but the best program and full therapeutic implications remain to be demonstrated.

## MANAGEMENT OF WILMS TUMOR

1. Diagnosis and management
    a. Three fourths present with palpable abdominal mass, usually smooth and rarely crossing midline (in contrast to neuroblastoma).
    b. One third present with abdominal pain, often associated with minor trauma and hemorrhage within tumor.
    c. Hypertension accompanies 25% to 60% of cases.
    d. Differential diagnosis includes other tumors and hydronephrosis or cystic disease.

### DIFFERENTIAL DIAGNOSIS: CHILDHOOD TUMORS

Malignant abdominal tumors
Renal: Wilms tumor, renal cell carcinoma
Neuroblastoma
Rhabdomyosarcoma
Hepatoblastoma
Lymphoma, lymphosarcoma
Benign abdominal masses
Renal: Renal abscess, multicystic dysplastic kidney, hydronephrosis, polycystic kidney, congenital mesoblastic nephroma
Mesenteric cysts
Choledochal cysts
Intestinal duplication cysts
Splenomegaly

    e. Abdominal ultrasound will diagnose most Wilms tumors and evaluate the retroperitoneum, liver, and vena cava for extension of disease.
    f. Screening serial renal ultrasounds are needed for patients with aniridia, hemihypertrophy, and Beckwith-Wiedemann syndrome at an interval of every 3 to 4 months.
    g. Four-view chest x-ray completes the metastatic workup.
    h. Angiography and cavography are rarely indicated; computed tomography (CT) may be helpful with very extensive lesions, detecting bilateral disease, and providing functional assessment of contralateral kidney.
        1) Complete blood count (CBC), urinalysis, serum creatinine, and urea nitrogen levels complete the preoperative testing; urine catecholamines help to rule out neuroblastoma.

2. Surgical treatment
    a. Exploration is carried out as soon as the child is stable, the previously mentioned studies are completed, and the situation is no longer considered an emergency.
    b. Transverse abdominal incision provides adequate exposure in most cases, from the tip of the twelfth rib on the involved side to the lateral rectus border on the opposite side.
    c. Exploration of the contralateral kidney with biopsy as needed should be carried out first; reflection of colon and complete mobilization of kidney are required for adequate visualization and manual inspection of front and back surfaces of the kidney.
    d. Resectability depends largely on the degree of attachment to the liver, duodenum, pancreas, spleen, diaphragm, abdominal wall, or major vascular invasion into the vena cava. Heroic extirpation involving major resection of these organs or cardiopulmonary bypass to remove high caval or atrial tumors is not warranted.
    e. Unresectable lesions should be treated with chemotherapy and reexplored; usually the tumor may then be removed. Pretreatment of large tumors reduces the rate of intraoperative rupture but does not influence and may alter histology (FH versus UH distinction). Because the preoperative diagnostic error rate has been 5% in the United States, routine pretreatment has not been recommended.
    f. Beginning the dissection along the posterior abdominal wall inferiorly and the great vessels medially, with early ureteral ligation, allows early exposure and ligation of renal vessels prior to mobilization of the mass.
    g. Biopsy of the tumor or localized operative spill does not upstage the tumor unless it is massive, in which case, whole abdomen irradiation is needed to avoid an increased incidence of abdominal recurrence. Largest relative risk for local recurrence in National Wilms Tumor Study (NWTS)-4 was observed in patients with stage III disease, those with UH (especially diffuse anaplasia), and those reported to have major tumor spillage during surgery.
    h. The adrenal is taken if the tumor involves the upper pole.
    i. Gross assessment of nodes has a 40% false-positive and 0% false-negative rate, and thus routine biopsy of hilar and

    periaortic nodes is warranted; radical node dissection does not influence survival but does improve staging. The absence of lymph node biopsy is associated with an increased relative risk of recurrence, which was largest in children with presumed stage I disease because of understaging.

   j. Remaining tumor in nodes or other organs should be marked with surgical clips to facilitate direction of radiation therapy.
   k. NWTS investigators found a 20% incidence of surgical complications, with the most common being intestinal obstruction and hemorrhage.
3. Staging (Table 28-1)
   a. Histopathology and tumor stage are the most important predictors of survival in Wilms tumor patients. The staging system has undergone refinement over the years as data have been examined with each NWTS study.
   b. In NWTS-3, the distribution by stage of FH tumors was stage I, 47%; stage II, 22%; stage III, 22%; and stage IV, 9%. Both the surgeon and pathologist have responsibility for determining local tumor stage.
4. Chemotherapy and radiation therapy are given in NWTS-5 according to Table 28-2.
   a. NWTS-4 demonstrated that a short administration schedule (6 months) of vincristine and dactinomycin is equally as effective as longer duration therapy (15 months) with respect to 4-year relapse-free survival (RFS).
   b. The use of single-dose (pulse-intensive) treatment with dactinomycin has an equivalent 2-year RFS to those treated with a standard 5-day regimen. Pulse-intensive drug administration provides for equal efficacy, greater administration dose intensity, and less severe hematologic toxicity.
   c. Patients with bilateral Wilms tumor (BWT) and/or nephrogenic rests should be managed with a nephron-sparing approach following primary chemotherapy. Those patients with anaplasia are at much greater risk for recurrence, so for them a renal-sparing approach is not beneficial.
   d. NWTS-4 included 5.6% of patients with bilateral Wilms tumor. The 8-year event-free survival for BWT with FH was 74%, and overall survival was 89%; the event-free survival for BWT with UH was 40%, and overall survival was 45%. Preservation of renal parenchyma is possible in many

TABLE 28-1 **Staging System of the National Wilms Tumor Study (NWTS)**

| Stage | Description |
|---|---|
| I | Tumor limited to the kidney and completely excised. The renal capsule is intact, and the tumor was not ruptured prior to removal. There is no residual tumor. The vessels of the renal sinus are not involved. |
| II | Tumor extends beyond the kidney but is completely excised. There is regional extension of tumor (i.e., penetration of the renal capsule, extensive invasion of the renal sinus). The tumor may have been biopsied, or there may be local spillage of tumor confined to the flank. Extrarenal vessels may contain tumor thrombus or be infiltrated by tumor. |
| III | Residual nonhematogenous tumor confined to the abdomen; lymph node involvement, diffuse peritoneal spillage either before or during surgery, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed |
| IV | Hematogenous metastases (lung, liver, bone, brain) or lymph node metastases outside the abdominopelvic region are present. |
| V | Bilateral renal involvement at diagnosis |

patients after initial preoperative chemotherapy. The incidence of end-stage renal disease remains significantly higher in children with BWT.

5. Treatment of relapses
   a. Variable prognosis based on initial stage, site of relapse, time from initial diagnosis to relapse, and prior therapy.
   b. Risk of tumor relapse in NWTS-3 at 3 years was 9.6%, 11.8%, 22%, and 22%, respectively, for stages I through IV. Relapses occurred in 36% of stage I through III and 45% of stage IV patients with UH.
   c. Adriamycin, dacarbazine, cisplatin, or higher doses of vincristine and/or cyclophosphamide (Cytoxan) are used to treat relapses.
6. Complications of therapy
   a. Bone marrow suppression, early or delayed radiation enteritis, bowel obstruction, hepatic dysfunction, scoliosis, radiation nephritis, interstitial pneumonitis, cardiomyopathy with congestive heart failure, and sterility

TABLE 28-2 **Protocol for National Wilms Tumor Study (NWTS)-5**

| | Radiotherapy | Chemotherapy Regimen |
|---|---|---|
| Stage I, FH < 24 mo and < 550 g tumor weight | None | None (only surgery for this group) |
| Stage I, FH > 24 mo and/or > 550 g tumor weight<br>Stage II, FH<br>Stage I, anaplasia | None | EE-4A (AMD plus VCR; 18 wk) |
| Stage III-IV FH<br>Stage II-IV, focal anaplasia | Yes[a] | DD-4A (AMD, VCR, and DOX; 24 wk) |
| Stage II-IV, diffuse anaplasia | Yes[a] | I(VCR + CPM + E; 24 wk) |
| Stage I-IV CCSK | Yes[a] | I as above |
| Stage I-IV RTK | Yes[a] | RTK (Carbo + E + CPM; 24 wk) |
| Stage V, bilateral: biopsy or limited surgery, both kidneys | | |
| Stage I or II, FH | | EE-4A as above |
| Stage III or IV, FH | | DD-4A as above |
| Stage I-IV, anaplasia | | I as above |

[a] Consult protocol for details regarding radiation therapy.

*FH,* Favorable histology; *AMD,* dactinomycin; *VCR,* vincristine; *DOX,* doxorubicin; *CPM,* cyclophosphamide; *CCSK,* clear cell sarcoma of the kidney; *RTK,* rhabdoid tumor of the kidney; *E,* etoposide; *carbo,* carboplatin.

   b. Secondary neoplasms are reported in 3% to 17% in 20- to 25-year survivors, especially in radiation fields.

7. Cooperative group trials
   a. Prospective randomized trials have been necessary to answer questions about optimal treatment. The Children's Cancer Study Group and the Pediatric Oncology Group collaborated within the National Wilms Tumor Study Group.
   b. Results of NWTS-3 are summarized in Table 28-3.
   c. NWTS-5 is focusing on correlating biologic parameters with the outcome of treatment of Wilms tumor. Genes on chromosome 11 may be responsible for induction of Wilms tumor. Loss of heterozygosity for a portion of

TABLE 28-3 **Results of the National Wilms Tumor Study-3**

| Stage | Histology | 4-Year Postnephrectomy Survival (%) |
|---|---|---|
| I | Favorable | 97 |
| II | Favorable | 92 |
| III | Favorable | 84 |
| IV | Favorable | 83 |
| I-III | Unfavorable | 68 |
| IV | Unfavorable | 55 |
| All patients | | |
| Unfavorable | | 89 |
| Clear cell sarcoma | | 75 |
| Rhabdoid sarcoma | | 26 |

*(Adapted from D'Angio CJ, Breslow N, Beekwith JB, et al:* Cancer *64:349–360, 1989. Reproduced from Snyder HM, D'Angio CJ, Evans AE, Raney RB: Pediatric oncology. In Walsh PC, Retik AB, Stamey TA, et al, editors:* Campbell's urology, *ed 6, Philadelphia, 1992, Saunders.)*

chromosome 16q in 20% of patients with Wilms tumor has been noted.

d. Expect to see the use of partial nephrectomies following chemotherapy for unilateral Wilms tumors in the future. Renal preservation therapy will be the goal in addition to maintaining relapse-free and cancer-specific survival rates.

# Neuroblastoma

## INCIDENCE

Neuroblastoma represents 8% to 10% of all childhood malignancies and is the most common malignant tumor of infancy. Following brain tumors, it is the most common malignant solid tumor of childhood. One third of cases are diagnosed in the first year of life and an additional one fourth between 1 and 2 years of age.

## ETIOLOGY

1. Arise from primitive, pluripotential sympathetic cells (sympathogonia) derived from neural crest
2. Ganglioneuromas and ganglioneuroblastomas also arise from neural crest cells.
3. Characterized cytogenetically by deletion of the short arm of chromosome 1

## PATHOLOGY

Gross tumors are lobular, tend to be infiltrative, and are often associated with stippled calcification. Histologically, neuroblastoma is one of the “small, round blue-cell tumors” of childhood. Tumors may form rosettes and exhibit neurofibrils if differentiation is good. Ultrastructure shows characteristic peripheral dendritic processes. There is a gradual degree of malignancy from neuroblastoma (most malignant) to ganglioneuroblastoma (intermediate) to ganglioneuroma (benign).

## LOCATION AND PRESENTATION

Neuroblastoma can arise anywhere along the sympathetic chain from the head to pelvis; more than half arise in the abdomen and two thirds of these in the adrenal. It presents as an irregular, firm, nontender, and fixed mass, often extending beyond the midline. Abdominal paravertebral sympathetic ganglion origin has an increased incidence of dumbbell-shaped intraspinal extension, which may produce signs of cord compression. Presacral tumors may result in urinary frequency, retention, or constipation. Cervical sympathetic tumors can cause Horner syndrome. Thoracic tumors may be asymptomatic or produce cough, dyspnea, or infection from airway compression. As many as 70% of patients have metastasis (liver is most common in younger children, bone in older children) at presentation. Unexplained fever, malaise, anorexia, weight loss, and irritability are common.

## DIAGNOSIS

The patient is anemic if the disease has disseminated. Bone marrow aspirate is indicated in all suspected cases: 50% to 70% positive. Ninety-five percent of patients have elevation of urinary catecholamines produced by tumor (vanillylmandelic acid and/or homovanillic acid). This can be checked on spot urine sample. Appropriate radiographic imaging will depend on the site. For abdominal tumors, intravenous pyelography, ultrasound, CT, and magnetic resonance (MR) contribute to staging the tumor and determining resectability. Chest x-rays, skeletal survey, and often bone scan are routine. Table 28-4 depicts minimum recommended tests for determining extent of disease.

TABLE 28-4 **Minimum Recommended Tests for Determining Extent of Disease Neuroblastoma**

| Tumor Site | Tests |
|---|---|
| Primary | Three-dimensional measurement of tumor by CT scan, MRI, or ultrasound |
| Metastases | Bilateral posterior iliac bone marrow aspirates and core biopsies (four adequate specimens necessary to exclude tumor) |
|  | Bone radiographs and either scintigraphy ($^{99m}$Tc-diphosphonate or $^{131}$I- or $^{123}$I) meta-iodobenzylguanidine (MIBG) or abdominal and liver imaging by CT scan, MRI, or ultrasound |
|  | Chest radiograph (AP and lateral) and chest CT scan |
| Markers | Quantitative urinary catecholamine metabolites (VMA and HVA) |

*AP,* Anteroposterior; CT, computed tomography; *HVA,* homovanillic acid; *MRI,* magnetic resonance imaging; *VMA,* vanillylmandelic acid.

## STAGING AND PROGNOSIS

1. The current, favored staging system is based on clinical, radiographic, and surgical evaluation of children with neuroblastoma. The International Neuroblastoma Staging System (INSS or Evans classification) provides for uniformity in staging of patients, facilitating clinical trials and biologic studies around the world (Table 28-5).
2. A histologic-based prognostic classification (Shimada) is formulated around patient age and the following histologic features:
   a. Presence or absence of schwannian stroma
   b. Degree of differentiation
   c. Mitosis-karyorrhexis index (MKI)
3. Retrospective evaluation of the Shimada method demonstrated that histologic patterns were independently predictive of outcome, whereas stage was prognostically less important.
4. A simplified system has been devised, which predicts a favorable outlook based on presence of calcification and a low mitotic rate (less than 10 mitoses/10 high-power field). The grading system was developed for finding tumors with both features (grade 1), the presence of only one of these features (grade 2), or absence of both features (grade 3). Combining

TABLE 28-5 **International Neuroblastoma Staging System**

| Stage | Description |
|---|---|
| 1 | Localized tumor confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically |
| 2A | Unilateral tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes; identifiable contralateral lymph nodes negative microscopically |
| 2B | Unilateral tumor with complete or incomplete gross excision; positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically |
| 3 | Tumor infiltrating across the midline with or without regional lymph node involvement; or unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral lymph node involvement |
| 4 | Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, and/or other organs (except as defined in stage 4S) |
| 4S | Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin, and/or bone marrow |

grade with age (less than 1 or older than 1 year) and surgicopathologic staging, low- and high-risk groups emerge. Further evaluation will take into account histologic modifiers, such as the level of serum ferritin, *N-myc* copy number, and tumor DNA content. *N-myc* amplification occurs in 25% to 30% of primary neuroblastomas from untreated patients, and amplification is associated primarily with advanced stages of disease.

5. Recognized mutations and structural alterations in specific genes contribute to inheritable predisposition to neuroblastoma and/or to aggressive disease pathogenesis, and implications for diagnosis and therapy. A new clinicomolecular risk score that incorporated fusion gene status (negative and PAX3/FOXO1 and PAX7/FOXO1 positive) intergroup rhabdomyosarcoma study TMM Stage and Age showed a significant increase in performance over the current risk stratification scheme. Thus gene signatures can improve current stratification of patients with RMS but will require complex assays to be developed and extensive validation before clinical application.

## TREATMENT

1. Complete surgical removal is the most effective form of therapy, which also allows for diagnosis, provides tissue for biologic studies and surgical stage of tumor, and allows for attempted excision of tumor. Based on INSS criteria, the operative protocol incorporates the following:
   a. Resectability of primary or metastatic tumor is determined in light of tumor location, mobility, relationship to major vessels, ability to control blood supply, and overall prognosis of patient.
   b. Nonadherent, intracavitary lymph nodes should be sampled.
   c. Routine biopsy of the liver in situations involving an abdominal neuroblastoma without evidence of metastatic disease has been advocated.
2. **Treatment of low-risk disease:** Treatment for patients with localized tumors consists most commonly of surgery alone but in some cases surgery combined with 6 to 12 weeks of chemotherapy. Chemotherapy consists of carboplatin, cyclophosphamide, doxorubicin, and etoposide. Doses are kept low to minimize permanent injury from the chemotherapy regimen.
3. **Treatment of intermediate-risk disease:** Children with metastatic disease to regional lymph nodes and infants with INSS stage 4 tumors comprise this group. Chemotherapy occurs for 12 to 24 weeks of the same chemotherapy as described previously. In addition, radiation therapy is utilized to enhance disease-free survival.
4. **Treatment of high-risk disease:** Patients with disseminated disease require intensive treatment with multiagent therapy of various combinations, but overall survival has remained disappointingly low (below 15%). The use of high-dose chemotherapy (carboplatin, cyclophosphamide, doxorubicin, etoposide, and ifosfamide with high-dose cisplatin), surgery, intraoperative radiation, and bone marrow transplantation has resulted in improved 2-year survival rates (Table 28-6).
5. Antibodies targeting GD2, a surface antigen found on the surface of neuroblastoma cells, have emerged as a major therapeutic development for high-risk neuroblastoma. Anti-GD2 antibodies incite immune-mediated cytotoxicity towards neuroblastoma cells when given as monotherapy or in combination with cytokines such as sargramostim (granulocyte macrophage colony-stimulating

TABLE 28-6 **Disease-Free Survival (2-Year) Based on Risk Category and Age**

| Risk Category | 2-Year Disease-Free Survival (%) | Patient Age (Years) | INSS Stage |
|---|---|---|---|
| Low | > 90 | All | 1 |
|  | 85 | All | 2A |
|  | 87-89 | < 1 | 2B/3 |
|  | 57-90 | < 1 | 4S |
| Intermediate | 59 | > 1 | 2B/3 |
|  | 75 | < 1 | 4 |
| High | 40/15[a] | > 1 | 4 |

[a] Difference relates to complete versus partial surgical resection, respectively.
INSS, *International Neuroblastoma Staging System.*

factor) or aldesleukin (interleukin-2). Responses to anti-GD2 agents appear most notable in patients with minimal residual disease following standard therapy. The standard approach to treating high-risk neuroblastoma is likely to undergo a major shift once an anti-GD2 antibody becomes commercially available.

## GU Rhabdomyosarcoma

Rhabdomyosarcoma arises from primitive totipotential embryonal mesenchyme. GU tract involvement occurs with the second greatest frequency after head and neck tumors. Sites include bladder, prostate, vagina, and cervix or paratesticular tissue. They comprise approximately 20% of all rhabdomyosarcomas. The incidence of GU rhabdomyosarcoma is 0.5 to 0.7 cases per 1 million children younger than 15 years.

### PATHOLOGY

1. A tumor arises from any site that develops from embryonic mesenchyme.
    a. Rhabdomyoblasts are the progenitor cell.
    b. Tumor subtypes differ based on extent of differentiation from mesenchymal progenitor.
    c. Classification system of Horn and Enterline based on primary histologic subtype: embryonal (60%); botryoid; alveolar (20%); spindle cell; and pleomorphic.
    d. New international classification system proposed by Intergroup Rhabdomyosarcoma Study (IRS) (Table 28-7)

TABLE 28-7 **Intergroup Rhabdomyosarcoma Study (IRS)-IV Staging**

| Stage | N | M | Tumor Location | T | Size |
|---|---|---|---|---|---|
| 1 | N0 or N1 | M0 | Favorable sites | T1 or T2 | a or b |
| 2 | N0 | M0 | Unfavorable site | T1 or T2 | a |
| 3 | N1 | M0 | Unfavorable site | T1 or T2 | a |
|  | N0 or N1 | M0 |  | T1 or T2 | b |
| 4 | N0 or N1 | M1 | Metastatic disease | T1 or T2 | a or b |

*T1,* Confined to anatomic site of origin; *T2,* extension and/or fixation to surrounding tissue; *Ta,* tumor less than 5 cm in greatest diameter; *Tb,* tumor is 5 cm or larger; *N0,* regional lymph nodes are not clinically involved; *N1,* regional nodes are clinically involved by tumor; *M0,* no distant metastases; *M1,* metastases are present. Genitourinary (GU) tumors considered to be favorable sites include the vulva and vagina. GU tumors considered to be unfavorable sites include the bladder, prostate, and uterus.

   e. Desmin and actin stains sometimes are useful in determining diagnosis.
   f. Genetic translocations between chromosome 1; 13 (favorable) and 2; 13 (very high risk) are prognostic markers for survival in patients with alveolar tumors with metastatic disease.

## PRESENTATION

1. Signs and symptoms are dependent on organ of involvement and size of the primary at initial assessment.
   a. Bladder or prostate-irritative voiding symptoms, urinary retention, incontinence, or infection. Trigonal involvement leads to hydronephrosis and progressive obstruction. Hematuria and constipation are also seen.
   b. Vagina-visible mass, hemorrhage, and vaginal discharge
   c. Paratesticular rhabdomyosarcoma presents as painless scrotal mass with two peak incidences at 3 to 4 months of age and again during teenage years.

## EVALUATION

1. Thorough assessment of both local and metastatic sites
   a. CT and ultrasound scan of abdomen and pelvis
   b. Lobulated soft tissue mass with homogenous echogenicity is seen on ultrasound.
   c. Transrectal ultrasonography can document involvement of prostate and facilitate biopsies.

2. CT is the most widely used modality for GU rhabdomyosarcomas. Use oral, rectal, and intravenous contrast.
3. Magnetic resonance imaging (MRI) with gadolinium-diethylenetriaminepentaacetic acid (DTPA) facilitates intravesical imaging and invasion into adjacent pelvic structures.
4. Accurate diagnosis can be based on histologic examination. Many GU tumors are amenable to endoscopic biopsy with cold cup forceps, either percutaneously, transvaginally, or transrectally.
5. Liver, lung, bone, bone marrow, and retroperitoneal nodes are most common sites for metastatic spread. Serum chemistries, including CBC and liver function tests, x-ray or CT of the chest, bone scan, and bone marrow biopsy are needed to complete evaluation.

## STAGING

1. IRS represents collaborative efforts from multiple institutions. IRS staging is dependent on resectability of primary tumor and status of draining lymph nodes.
2. Group 1: Local disease (without lymph node involvement) that has been completely removed both grossly and microscopically.
3. Group 2: Tumors grossly removed but residual microscopic disease (2A), regional nodal involvement with no microscopic residual disease (2B), or both nodal involvement and residual disease (2C).
4. Group 3: Incomplete removal of gross disseminated disease
5. Group 4: Distant metastatic involvement present

This system is dependent on the extent of surgical resection. The IRS-IV staging system (TNM) has been designed to overcome some of these shortcomings. The most important change is the inclusion of pretreatment stage (Table 28-8), rather than surgical staging alone.

## INTERGROUP RHABDOMYOSARCOMA STUDIES

1. The collective experience of a number of institutions was needed to assess a growing number of treatment options. IRS-I determined that:
   a. Postoperative radiation therapy of the tumor bed was helpful in group 1 patients.

TABLE 28-8 **IRS-IV Staging and Treatment of Paratesticular Rhabdomyosarcoma**

| Clinical Group | Tumor Status | Therapy |
|---|---|---|
| 1 | Tumor completely excised[a] (not alveolar subtype) | Vincristine and actinomycin D for 1 year[b] |
| 2 | Tumor excised with microscopic residual disease at margin and/or positive lymph nodes involving ipsilateral hilar-para-aortic chain | Vincristine plus actinomycin D plus cyclophosphamide versus vincristine plus actinomycin D plus ifosfamide for 1-2 years plus radiation therapy to involved region[c] |
| 3 | Gross residual local and/or regional disease (retroperitoneal nodes) that is not surgically removable | 3- to 7-drug regimen plus radiation therapy to involved region[d] |
| 4 | Distant metastasis | Same as group 3 |

[a] If there has been scrotal contamination, hemiscrotectomy and relocation of the contralateral testis into the thigh are advised to avoid the effects of local radiation on the remaining gonad.

[b] No radiation.

[c] Conventional radiation.

[d] Conventional or hyperfractionated radiation.

   b. Chemotherapy with vincristine, actinomycin D, and cyclophosphamide (VAC) was superior to vincristine and actinomycin D alone (VA) in group 2 patients.
   c. Pulse VAC following initial irradiation in groups 3 and 4 was beneficial.
   d. Adriamycin provided additional benefit in those with advance disease (groups 3 and 4).

2. With the favorable results achieved in IRS-I, IRS-II (1978 to 1984) determined the feasibility of primary chemotherapy. Following biopsy-proven rhabdomyosarcoma, VAC therapy was initiated, response documented, and chemotherapy continued for 16 weeks. The residual mass was resected and chemotherapy continued for 2 years. Radiation therapy was added for gross or microscopic disease following resection.

3. IRS-III (1984 to 1988) addressed five specific issues regarding chemotherapeutic protocols and response to therapy. More aggressive chemotherapeutic protocols were used in patients with UH (alveolar, anaplastic, and monomorphous types). The use of second- and third-look surgery to assess response in groups 3 and 4 would lead to improved local control.

The results of IRS-III proved superior to IRS-I and II. There was a 60% salvage rate of functioning bladder at 4 years from diagnosis, compared to only 22% and 25% in prior studies. Mortality in patients with disseminated disease (groups 1 through 3) declined to less than 10%.

## TREATMENT

1. In IRS-IV, VAC was shown to be as effective as two other three-drug regimens (VIE/VAE-ifosfamide, etoposide). In IRS-V, low-risk patients are randomized to receive either VA or VAC, ± x-ray therapy (XRT). Intermediate-risk patients received chemotherapy and XRT and are randomized to VAC or VAC alternating with vincristine, topotecan, and cyclophosphamide. High-risk patients received CPT-11 (irinotecan, VAC, and XRT).
2. In IRS-IV, hyperfractionated radiation therapy did not achieve better results than conventional radiation therapy. For IRS-V, patients with group 1 embryonal pathology will not receive XRT. For other patients, the dose of radiation to residual primary will be higher than to microscopic residual disease, and metastasis will be irradiated as well. Surgery as treatment of gross residual disease after chemotherapy is still an option.
3. The IRS is now known as the Children's Oncology Group Soft Tissue Sarcoma Committee. Recent analysis of 65 patients with Enbrel nonmetastatic bladder/prostate rhabdomyosarcoma were analyzed. Local therapy with radiation and/or surgery was performed based on age, tumor size, and response. Eighty-nine percent of the patients had IRS Group 3 disease. Five-year overall survival for the whole group was 76%, and the 5-year event-free survival was nearly 70%. Local therapy remains an important factor for prognosis of localized Enbrel

bladder/prostate rhabdomyosarcoma. Inadequate primary or secondary surgery compromises the outcome and should be avoided. Radiotherapy alone, complete surgical tumor resection, or combined preoperative radiotherapy with surgical resection lead to similar good local control rates and prognosis.

### RELAPSE

Five-year survival after relapse is 64% for botryoid embryonal, 26% for other embryonal, and 5% for alveolar or undifferentiated pathology. Lower stage embryonal lesions portend improved survival after relapse: 52% stage I, 20% stage II and III, and 12% stage IV.

### COMPLICATIONS

1. Hematologic complications similar to those seen with the same drugs in Wilms tumor therapy occur.
2. The high radiation dose required to control this tumor often produces severe proctitis and fibrosing cystitis, which may destroy normal bladder function and complicate any subsequent surgery such as reconstruction.

## Testis Tumors

Testis tumors are uncommon in children, accounting for approximately 1% to 2% of all pediatric solid tumors. Incidence in children is 1 per 100,000. Peak incidence is at 2 years of age; children have more benign tumors and fewer germinal testis tumors than do adults.

### CLASSIFICATION

1. Classification has been debated (Table 28-9).
2. Germinal tumors constitute only approximately 77%, compared with 95% of testis tumors in adults.
   a. Yolk sac carcinoma (embryonal carcinoma, endodermal sinus tumor, orchioblastoma) comprises approximately 39% to 62% of all testis tumors in children. Yolk sac carcinoma rarely (4%) spreads to retroperitoneal nodes; it more frequently (20%) spreads to lungs, especially in children older than 1 year. Alpha fetoprotein (AFP) is elevated 90% of time. Average age of presentation is 3 years.

TABLE 28-9 **Classification of Prepubertal Testis Tumors**

| | | |
|---|---|---|
| I | Germ cell tumors | Yolk sac tumor<br>Teratoma<br>Mixed germ cell<br>Seminoma |
| II | Gonadal stromal tumors | Leydig cell<br>Sertoli cell<br>Juvenile granulosa cell<br>Mixed |
| III | Gonadoblastoma | Fibroma |
| IV | Tumors of supporting tissues | Leiomyoma<br>Hemangioma |
| V | Lymphomas and leukemias | |
| VI | Tumorlike lesions | Epidermoid cyst<br>Hyperplastic nodule attributable to congenital adrenal hyperplasia |
| VII | Secondary tumors | |
| VIII | Tumors of the adnexal | |

   b. Teratoma constitutes approximately 14% and is a uniformly benign tumor in children younger than 2 years, even when histology appears malignant.
   c. Seminoma is extremely rare before puberty and in essence should be considered a postpubertal tumor.
3. Nongerminal tumors (stromal tumors) present most often at age 4 to 5 years.
   a. Interstitial cell (Leydig cell) tumors are approximately 18% of all testis tumors, usually virilizing or virilizing with gynecomastia (rarely malignant). Must be differentiated from hyperplasia (nodules that develop in testes of boys with poorly controlled congenital adrenal hyperplasia). Leydig tumors are unresponsive to adrenocorticotropic hormone (ACTH) and dexamethasone and gonadotropin stimulation.
   b. Gonadal stromal (Sertoli cell) tumors are approximately 8% of all prepubertal testis tumors; they are usually present as a painless mass and are rarely malignant.
   c. Paratesticular rhabdomyosarcoma constitutes approximately 4% of testis tumors in children.

Reticuloendothelial malignancy, primarily lymphomas and leukemias, may present with testicular secondary tumor in 2% to 3%. Patients with leukemias rarely present with a testicular mass and no evidence of systemic disease.

## EXAMINATION

Although all boys with a testis mass will come to surgical exploration through the groin, a careful preoperative evaluation should be carried out. If it suggests a tumor is benign, the tumor may be removed with preservation of the gonad.

1. Scrotal ultrasound should be done in most cases; it helps to establish that the testis is abnormal with or without the presence of hydrocele. If calcium and cysts are present, a benign teratoma is suggested. A hypoechoic pattern is characteristic of leukemia or lymphoma.
2. Four-view chest radiographs should be done, with chest CT to follow any suspicious area.
3. CT is a mainstay of retroperitoneal evaluation, although ultrasound can also be useful.
4. All children should have AFP determined because it is a marker of yolk sac tumor.

## ENDOCRINE EVALUATION

1. In cases of Leydig cell tumor, urinary 17-ketosteroids are evaluated. Chorionic gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are normal or low. Height, weight, bone age, and pubertal changes are advanced.
2. Sertoli cell tumors exhibit normal or elevated estrogens and androgens in urine and serum; 17-ketosteroids are normal, as are gonadotropins.

## MANAGEMENT

1. Radical inguinal orchiectomy is standard unless preoperative evaluation suggests benign tumor with testis-sparing; local resection may be carried out.
2. Staging is similar to that of adult testis tumors (Table 28-10).
3. Yolk sac tumor
    a. For those patients with organ-confined yolk sac tumor, AFP will fall rapidly to normal. If the CT scan is negative, close

TABLE 28-10 **Intergroup Staging System for Testicular Germ Cell Tumors**

| Stage | Extent of Disease |
|---|---|
| I | Limited to testis (testes), completely resected by high inguinal orchiectomy: no clinical, radiographic, or histologic evidence of disease beyond the testis; tumor markers normal after appropriate half-life decline (AFP, 5 days; ß-hCG, 16 hours); patients with normal or unknown tumor markers at diagnosis must have a negative ipsilateral retroperitoneal node sampling to confirm stage I disease |
| II | Transscrotal orchiectomy: Microscopic disease in scrotum or high in spermatic cord (≤ 5 cm from proximal end); retroperitoneal lymph node involvement (≤ 2 cm) or persistently elevated increased tumor markers |
| III | Retroperitoneal lymph node involvement (≤ 2 cm), but no visceral or extraabdominal involvement |
| IV | Distant metastases, including liver |

*AFP,* Alpha fetoprotein; *hCG,* human chorionic gonadotropin.

surveillance is the treatment of choice. Monitoring should include monthly AFP and chest x-ray for the first year, then bimonthly during the second year. CT scan of the chest and abdomen may also be obtained every 3 months for the first year and every 6 months for the second year (varies by institution).

b. Approximately 15% of children will present with metastatic disease. For those with stage II disease, both retroperitoneal lymph node resection (RPLND) and chemotherapy have been used alone and in conjunction. No clear consensus exists on the optimal treatment because the number of cases is too few from which to draw valid conclusions.

c. Metastatic disease has been treated with VAC or cisplatin, bleomycin, and vinblastine. Children with hematogenous metastatic disease have been treated with combination regimens, with salvage rates approaching 100%.

d. RPLND should be reserved for patients with a nonbulky tumor mass confined to the retroperitoneum or for persistently elevated AFP levels anytime following orchiectomy without evidence of disease elsewhere.

4. Mature teratomas in the prepubescent male warrant a partial orchiectomy in which the cord can be cross-clamped and the tumor shelled out for frozen-section examination with testicular preservation. Metastases from such a mature teratoma have never been reported in children.
5. Gonadal stromal tumors (Leydig, Sertoli) are thought to be benign in almost all cases and are treated with orchiectomy alone. Tumors have ultrasound appearance of an intraparenchymal, homogenous, hypoechoic lesion. Enucleation of the tumor is a possible alternative to radical orchiectomy. Regression of virilizing signs is unpredictable.
6. Epidermoid cysts, which are hormonally inactive and usually present as a smooth, firm intratesticular mass, can be treated with testis-sparing surgery. The benign nature suggested by physical examination, serology, and ultrasound requires confirmation by a frozen section before organ sparing can be performed safely.
7. Reticuloendothelial tumors are managed by biopsy and systemic therapy.

## PROGNOSIS

1. More pediatric than adult testis tumors are benign.
2. Children younger than 2 years with yolk sac tumors have approximately a 90% chance of survival. The prognosis is worse in older children.
3. Tumor registry for pediatric testis tumor has been developed by the Urologic Section of the American Academy of Pediatrics. Therapy continues to evolve.

## CLINICAL PEARLS

1. **Wilms tumor** — The MWTS studies have allowed for refinement in the oncologic management of patients with Wilms tumor. The response to chemotherapy often is dramatic, so that there is consolidation of the tumor making surgical resection easier. The notion of performing nephron-sparing surgery has become routine for adult renal tumors, and this fact is being increasingly scrutinized for pediatric patients with Wilms tumor.
2. **Neuroblastoma** — Neuroblastoma remains the most common extracranial solid cancer in childhood that displays marked heterogeneity, from low- to high-risk tumors. Those with high-risk disease can be

*(Continued)*

## CLINICAL PEARLS—*cont'd*

difficult to treat with even the most intensive multimodal therapies achieving only 30% cure rates.

3. **Genitourinary (GU) rhabdomyosarcoma** — The evolution in the management of GU rhabdomyosarcoma has involved a marked decrease in the radical surgeries that were commonly performed in the past. The key is making a histologic diagnosis with biopsy, beginning aggressive chemotherapy, and then assessing radiographically for a decrease in tumor size. Surgical resection can then provide accurate staging of the patient, with some situations lending themselves to endoscopic resection of the tumor to attempt to spare organs. In younger children, avoiding radiation therapy, particularly to the pelvis, can be beneficial to prevent both short-term and long-term morbidity.
4. **Testis tumors** — Pediatric testis tumors with an elevation of alpha fetoprotein (AFP) generally denote yolk sac carcinoma and require orchiectomy. Other prepubertal testes that are not associated with elevation of AFP may be amenable to partial orchiectomies or enucleation if a discreet lesion is noted. Once a patient demonstrates pubertal changes and is found to have a potential testicular teratoma, then radical orchiectomy is indicated as opposed to performing a testis-sparing procedure.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Describe the approach taken for a 2-year-old child who presents with bilateral Wilms tumors.*
2. *Neuroblastoma involving the cervical ganglia can cause Horner syndrome. How else can neuroblastoma present?*
3. *Prostatic rhabdomyosarcoma (RMS) can cause urinary retention or constipation. How would a 4-year-old child who is found to have a prostatic RMS be evaluated and managed?*
4. *Vaginal RMS can present in toddlers as blood noted in the diapers. What would you tell the family of a 2-year-old girl who is discovered to have sarcoma botryoides that is confined in her vagina?*
5. *What is your evaluation of an 8-month-old boy who presents with a scrotal mass that does not transilluminate? If a yolk sac tumor is diagnosed and there is no evidence of retroperitoneal involvement, what is recommended for treatment and follow-up?*

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## CHAPTER 29

# Pediatric Voiding Function and Dysfunction

Stephen A. Zderic, MD

## The Normal Voiding Cycle

1. Bladder filling proceeds under conditions of low storage pressures.
2. At a certain volume, the sensation of fullness is noted.
3. The Barrington nucleus removes its inhibitory influences.
4. The sacral reflex arc is activated.
5. With detrusor contraction, intravesical pressure rises.
6. This sustained rise in detrusor pressure is accompanied by a funneling of the bladder neck and a relaxation of the striated external sphincter.

### NEONATE AND INFANT

1. In the traditional view, neonates and infants voided to completion via activation of the sacral reflex arc, and it was assumed that there was no suprasacral control of micturition at this time.
2. **It is now accepted that neonates and infants have some degree of suprasacral control over micturition based on the following observations:**
    a. Evidence for residual urine on voiding cystourethrography (VCUG).
    b. Evidence of a contracting striated external sphincter on VCUG.
    c. Evidence of postvoid residuals following spontaneous voids.
3. Voiding in the neonate and infant is related to the sleep cycle. Sillén has shown that 90% of neonates and infants will awaken from sleep in the minute preceding micturition.

## Basic Embryology

1. The urinary bladder and rectum arise from the primitive hindgut, which is partitioned by the urorectal septum.
2. The bladder and rectum share a substantial overlap in sensory innervation from the S2, S3, and S4 sacral segments.
   a. Clinical relevance: Constipation is often seen in patients with voiding dysfunction, and treating the constipation often cures the voiding symptoms.
3. The ureteral buds develop from the wolffian ducts and penetrate the blastema to start formation of the kidney.
4. In females, the ureteral bud takes off from the wolffian duct and may enter the lower urinary tract in an ectopic position that is distal to the urinary sphincter. Locations for such an ectopic ureter include the urethra, periurethral folds, or vagina along the lines of the Gartner ducts.
   a. Clinical relevance: In young females, suspect an ectopic ureter as a possible anatomic cause of their severe and continuous urinary incontinence.

## Anatomy and Physiology

1. The cortex is involved in the perception of bladder fullness and, in the mature child and adult, exerts volitional control over micturition by regulating the pontine micturition center.
2. The sensation of a full bladder has been localized to the pons, midcingulate cortex, and the bilateral prefrontal area using positron emission tomography (PET) scanning (although these studies were in adults and not in infants).
3. Coordination of micturition is centered in the brain stem in a cluster of neurons referred to as the *Barrington nucleus*.
4. Under conditions of bladder storage, neurons descending from the Barrington nucleus carry a stream of inhibitory signals to the reflex arc located in the sacral segments at S2, S3, and S4.
5. With bladder filling, afferent sensory nerves enter the posterolateral region of the sacral segments. These synapse with a short interneuron, which crosses the cord to synapse with the motor nuclei in the anterior horn.

6. The activity of this interneuron is modulated by descending influences from the Barrington nucleus in the brain stem. With the loss of the tonic inhibitory influences, the motor neuron is activated, and voiding is initiated with the contraction of the detrusor.
7. The contraction of the detrusor is mediated by acetylcholine binding to muscarinic receptors. The $M_3$ and $M_4$ subtypes are found in bladder.
8. Concurrent with the rise in detrusor pressure, there must also be a funneling and opening of the bladder neck. This process is under autonomic control, and this region of the bladder is rich in alpha-adrenergic receptors. It is also a region of the bladder that is rich in nitric oxide (NO) synthase; multiple studies have shown that NO serves as an important neurotransmitter in this area.
9. Concurrent with the rise in detrusor pressure, there must also occur a relaxation of the striated external sphincter located distal to the bladder neck. These striated muscle fibers are under voluntary control.
10. The striated external sphincter contractions are mediated by the neurotransmitter acetylcholine, which binds to nicotinic receptors.

### TRANSITIONAL PHASE

1. In time, the toddler begins to gain the sensation of bladder distention with filling.
2. The toddler begins to spend more time in the storage phase.
    a. Parents will report an increase in the number of dry diapers.
    b. Parents may note dry diapers in the morning.
3. Bladder capacity begins to increase.
    a. Increased urinary volumes
    b. Increased time of storage
4. Bowel continence appears.
5. The toddler expresses an interest in the commode.
6. A preference is expressed by the child for underwear.

### MATURATION

1. Even in the middle phases of the transition, a child may be dry by day, and yet the voiding cycle is incomplete.
2. The child has learned to fire the external sphincter to prevent an episode of incontinence.
3. Often the child is also contracting the external sphincter during voiding phase and thus fails to empty completely.
4. In time, there is better "fine tuning" of the voiding cycle by the child, and continence is achieved with a minimal post-void residual urine.

## Clinical Manifestations of Voiding Dysfunction

**Pediatric patients with voiding dysfunction present across a wide spectrum.**

1. Urinary tract infections
    a. Cystitis
    b. Pyelonephritis
    c. Associated with reflux
2. Infrequent voider
3. Daytime incontinence
4. Diurnal incontinence
5. Nocturnal enuresis

The degree of symptoms spans a spectrum from:

1. Mild dysfunctional voiding—occasional "accident"
2. Severe dysfunctional voiding—Hinman syndrome

### HINMAN SYNDROME

1. Severe detrusor sphincter dyssynergia
2. Neurologically intact—normal clinical exam and magnetic resonance imaging (MRI) of spinal cord
3. Incontinence—often day and night
4. Fecal soiling
5. Recurrent cystitis
6. Pyelonephritis vesicoureteral reflux
7. In extreme cases, may progress to renal failure

## The Clinical Approach to the Patient

The efficient management of the pediatric patient with voiding dysfunction calls for a clear strategy that begins by gathering information, an assessment of severity, and the formulation of a therapeutic plan. Despite the technologic age we practice in, this process must begin with a careful history. **In cases where simple therapies have failed, the history must always be revisited.**

### HISTORY

Physicians must approach such visits with ample time and patience. Time and again, families and patients will give us a first-rate history if we simply let them speak in their words and at their pace. (Dr. A. Barry Belman has coined the term *audio-uro-dynamics* for this procedure.) Simply giving the family and patient free rein and "letting them go" will provide many of the answers we seek. For some families, this may seem daunting, and a prompt, such as, "How does your child's bladder problem affect you on a car trip or a visit to the mall?" will get them to relay the information needed ***in their terms***. This may at times be much easier said than done within a busy clinic. However, we all need to be reminded that ***an ounce of active listening validates the family's concerns*** **far more than a pound of hastily given therapy,** no matter how accurate it may be. All of us need to remember that among our seemingly endless stream of day and night wetters lurks the rare patient (1% to 3%) with an ectopic ureter or a posterior urethral valve whose cure and well-being can only be ensured by a surgical procedure.

## QUESTIONS A CONSULTING PHYSICIAN MUST CONSIDER

1. Gender
2. Age of patient
3. Age at which training was attempted
4. Was the patient ever dry?
5. Do parents ever remember a dry diaper?
6. Fluid intake: Is your child thirstier than other children of the same age?
7. What is the child's maximal dry interval?
8. How frequently does your child void?
9. Does your child make a last-minute rush to get to the bathroom (urgency)?
10. Does your child ever squat en route to the bathroom? (Vincent's curtsy—on occasion a parent will demonstrate this maneuver in which the child stops an episode of urgency by dropping down and tucking the heel into the perineum to create a compression.)
11. What does it sound like when your child is urinating? Many parents will relay the classic features of a starting-and-stopping staccato stream characteristic of detrusor sphincter dyssynergia.
12. Is your child constipated?
    a. Frequency of stooling
    b. Are the stools hard or soft?
    c. Is defecation painful?
    d. Is there fecal soiling of the underwear?
13. Is urination painful?
14. Has your child ever had a urinary tract infection?
    a. If yes, was this associated with a high fever?
    b. How was the urine specimen collected (bag, voided, or catheter)?
15. Have any radiology studies been done?
16. Was your child imaged with in utero sonography? Keep in mind that most (although not all) major congenital obstructive uropathies will be detected in utero. For many expectant mothers, only one sonogram is performed at the 19- to 22-week time point. Although this screening sonogram will pick up major problems, hydronephrosis may be progressive, and prenatal sonography demands high-quality equipment and an experienced observer.

17. Is there a history of maternal diabetes? In such cases, the child is at risk for the development of sacral agenesis and may present some time later with a neurogenic bladder.
18. General social developmental questions should include:
    a. Any history of developmental delay
    b. Grade in school
    c. Scholastic performance
    d. Social stressors (death of family member or friend, divorce)
19. What are the restrooms at school like?
    a. Does your child have unrestricted bathroom privileges?
    b. Are the restrooms safe?
20. Does your child wet the bed? How many nights within a week or month?
21. Is your child difficult to arouse from sleep?
22. Does your child snore? How loud? Does your child ever stop breathing at night and awaken only to fall back into a deep sleep? Is your child falling asleep during the daytime hours?

## SELF AND FAMILY ASSESSMENT TOOLS

These are also critical measures at the time of intake. Some practices mail an information packet to a family whose child is being scheduled for a wetting complaint. The packet includes a voiding diary and a self-assessment tool that translates into a symptom score.

These additional self-reported data that should be reviewed by the physician include:

1. Voiding and elimination diaries
    a. Times of voids
    b. Volumes
    c. Fluid intake
    d. Bowel habits
2. Voiding questionnaire with scoring system: At least two such questionnaires have been developed for voiding dysfunction and serve as a pediatric version of the American Urological Association (AUA) symptom score. These scales provide a practitioner with a sense of how many resources a patient will require during therapy. In addition, if a patient's score fails to improve, these scores may indicate the need for more advanced, expensive, and invasive testing.

## THE PHYSICAL EXAMINATION

1. General appearance—evidence of neurologic or developmental issues?
2. Unusual facies (downturn of smile)—Ochoa syndrome—described by Dr. Ochoa as an inherited syndrome of urinary and fecal incontinence. The pontine micturition center is localized near the cranial nerves controlling facial expression, which accounts for this association. Autosomal recessive and localized to chromosome 10q23–24 and has been mapped to an area corresponding to the heparanase 2 gene (HPSE2, OMIM entry #613469).
3. Gait and general neurologic assessment—Does the patient favor one limb over another? Do the shoes wear evenly?
4. Spine—a careful exam of the lumbar sacral region is crucial. Look for lipomas, hair tufts, or dimpling in this region. These are clues to the possible presence of a tethered cord.
5. Abdomen—distended from constipation?
6. Genitalia
7. In female patients, check for continuous leakage; if this is present, suspect ectopic ureter.

### Observe the Patient Void

**Direct observation of a void can be crucial.** A patient who is voiding normally should be able to converse with ease. In contrast, a thin and weak yet steady stream with the patient unable to converse while applying a Valsalva maneuver would be indicative of a possible stricture. In contrast, a staccato stream with a start-and-stop pattern would be indicative of striated detrusor sphincter dyssynergia.

## LABORATORY TESTING

The following lab studies are inexpensive and may be read from a dipstick analysis in the office and provide useful clues:

1. Urinalysis
   a. Urine culture—to be ordered if the urinalysis is positive for leukocytes and nitrates

2. Urine specific gravity

   In severe cases with abnormal imaging or recurrent pyelonephritis, blood urea nitrogen (BUN) and creatinine (Cr) should be checked.

## IMAGING

In many instances, no imaging is needed. A well done history and physical followed by simple recommendations such as a timer watch and a voiding diary and treatment of constipation (if it is present) are all that are required to produce continence. **However, in selected cases, imaging should be obtained beginning with the more simple, less invasive, and less expensive studies and proceeding to the more invasive and advanced studies only if required.**

1. **Kidney ureter bladder (KUB) x-ray—**a simple and inexpensive study that demonstrates for physician, family, and patient alike the presence of significant constipation. **This is probably the most imaging the majority of these patients will need unless there is an associated history of urinary tract infections.**
2. **Ultrasound—**increased expense but noninvasive. It offers the benefit of reassurance to physician, patient, and family that the anatomy is set correctly. It is okay to have a lower threshold for ordering an ultrasound given that it is profoundly frustrating for a family and patient to attempt behavioral management methods for a long time, only to discover after months of futility that the underlying problem was anatomic. **It is critical to order an ultrasound in situations in which one suspects anatomic incontinence in a female on the basis of ectopic ureter.**
   a. Suspect ectopic ureter based on:
      1) Hydronephrosis most often in upper pole system
      2) Dilated ureter behind the bladder with ureter dropping below the level of the bladder neck
   b. Must include renal *and* bladder views
   c. Although rare, even a well done ultrasound may miss an ectopic ureter. If the history is compelling enough, further imaging with an MRI or IVP (intravenous pyelogram) is warranted. (MRI-IVP is more sensitive than intravenous urography in this setting.)
3. **VCUG—**increased expense, invasive, and potentially traumatic to the child. **Today there is a growing movement to limit the**

**number of VCUGs being done** except in those cases in which there simply is no alternative to searching for vesicoureteral reflux or excluding bladder outlet obstruction. Indications for a VCUG study in patients with voiding dysfunction are:

a. Febrile urinary tract infection
b. A male patient with a thick-walled bladder and upper tract changes to rule out the presence of posterior urethral valves or a urethral stricture

### Imaging That Is Less Frequently Indicated for Voiding Dysfunction

1. **IVP**—This study was the gold standard for detecting the presence of ectopic ureters and duplication anomalies. Certainly in the presence of adequately functioning renal parenchyma, contrast will accumulate within a dilated system that provides a clue of possible ectopia. *Delayed views are essential, and this study must be monitored closely by the radiologist and the urologist ordering the study*. Failure to obtain the proper views will render the study worthless, hence the importance of communication between urologist and radiologist.
2. **Computed tomography (CT) scan or MRI-IVP**—In recent years advances in technology have expanded the use of rapid scanning using either the CT scan or MRI, and these have been applied to the search for ectopic ureters. **For small, poorly functioning systems, the use of the CT with contrast or MRI with gadolinium will allow for detection of contrast within nondilated ureters that can escape detection with sonography or a conventional IVP.**
3. **Lumbar-sacral MRI**—This study is indicated for any patient with focal neurologic signs (abnormal gait, foot drop) or findings on examination of the lumbar sacral spine (hair tuft, lipoma, abnormal dimple). In the absence of these findings and in situations in which the patient is failing to improve, this study may also be considered to rule out a tethered cord.

## URODYNAMIC MEASUREMENTS

1. **Uroflow and measurement of postvoid residual with handheld ultrasound unit.** This simple and easy-to-use technique is complementary to direct observation of the void. A sawtooth flow pattern suggests the firing and relaxation of the

external sphincter seen with classic dysfunctional voiding. A slow, flat, and prolonged curve suggests outflow obstruction on an anatomic basis. **For most patients, this is the only urodynamic study needed.**

2. **Cystometrogram—**indicated to rule out uninhibited bladder contractions. While the administration of anticholinergic medications may be initiated on an empiric basis, cystometry should be done prior to botulinum toxin (Botox) therapy into the detrusor, which is an invasive procedure.
3. **Videourodynamics—**indicated to rule out uninhibited contractions and also to assess the bladder neck in complex cases.

In our experience, cystometry and videourodynamics are rarely indicated in the assessment of pediatric voiding dysfunction. **These studies will usually be limited to less than 5% of patients presenting to a pediatric voiding dysfunction clinic and should be restricted to those patients who fail the basic treatment protocols or anticholinergic therapy or those in whom internal sphincteric dyssynergia is suspected.** This is in marked distinction to those patients in whom a clear-cut neurogenic bladder is present as in spina bifida patients, all of whom must undergo urodynamic testing. When urodynamic or videourodynamic studies are indicated, the best information will be obtained when the urologist ordering the study is present and communicates with the patient so as to best recreate in the laboratory setting the symptoms that the patient is experiencing.

## Treatment of Dysfunctional Voiding and Elimination by Category

Selection of the optimal treatment calls for an understanding of the cycle of failure (Figure 29-1). Based on this, one can begin to design a program for the patient that addresses the patient's unique needs.

### URINARY TRACT INFECTIONS

For many patients the sole manifestation of voiding dysfunction is recurrent cystitis. A careful voiding history often reveals a patient who is dry by day and night but who voids infrequently

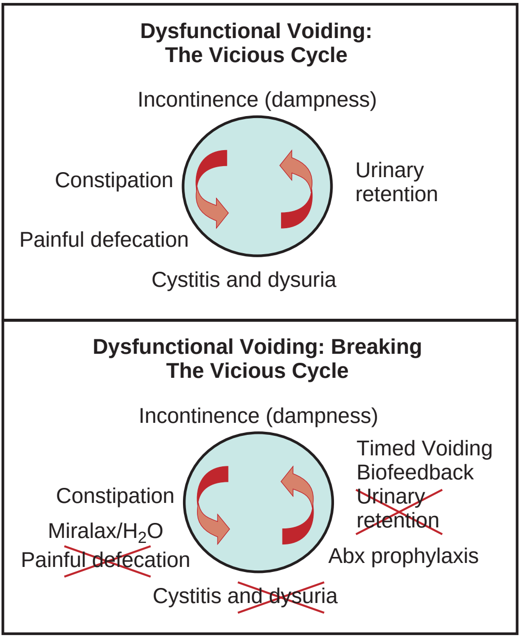

FIGURE 29-1 The cycle of dysfunctional voiding in which constipation leads to cystitis and dysuria, followed by retention and wetting, and the “menu” of choices by which the cycle is broken.

(two to three times per day), has poor water intake, and is constipated. Treatment should consist of:

1. Timed voiding regimen (2-hour intervals)
2. Voiding logs
3. Timer watch
4. Antibiotic prophylaxis
5. Increased free water intake
6. Treat associated constipation.

## INFREQUENT VOIDER

These patients may void two to three times per day and often present with dampness as the primary complaint. In many instances, these are high-achieving children who just cannot break away from what they are doing to “listen to their bladder.” In other instances, these children are reluctant to use the restrooms at school because of fear of sanitation and/or safety.

1. Timed voiding regimen (2-hour intervals)
2. Voiding logs
3. Timer watch
4. Treat associated constipation.
5. Note to school nurse or teacher for unrestricted bathroom privileges

## CONSTIPATION

**Constipation is the enemy of continence.** Time and again patients present with mild to moderate voiding dysfunction and/or urinary tract infections with significant constipation, and on institution of a bowel regimen all voiding complaints cease. Treatment should consist of:

1. Increase fruits and vegetable intake
2. Fiber-based cereals
3. Increase water intake
4. Stool-softening regimens
    a. Lactulose
    b. MiraLAX
5. Enemas
    a. Administered per rectum
    b. Antegrade administration of enema via surgically created appendiceal access for medically refractory cases (antegrade colonic enema [ACE] procedure)

## DYSFUNCTIONAL VOIDING WITH DETRUSOR SPHINCTER DYSSYNERGIA

For patients in whom the diagnosis of detrusor sphincter dyssynergia is suspected, confirmation with a uroflow may be helpful to confirm the rising and falling flow rate. There are two types of detrusor sphincter dyssynergia to consider, and their treatments differ markedly.

### Striated External Sphincter Dyssynergia

This is the most common form.

1. Timed voiding
2. Voiding diary
3. Timer watch

4. Treat constipation if present.
5. Biofeedback therapy to coach the patient into relaxing the pelvic floor

Only if these less invasive means of treatment fail, would one proceed to these remaining options, usually following a carefully performed videourodynamic assessment.

1. Clean intermittent catheterization
2. Cystoscopy and direct injection of Botox into striated external sphincter

### Internal Sphincteric Dyssynergia

**This is the less common form.** These patients demonstrate a diminished flow rate with a flattened curve. To make this diagnosis accurately, videourodynamics are helpful. The low flow rate, silent pelvic floor electromyogram (EMG), and increased voiding pressures correlate with the closed bladder neck on fluoroscopy to clinch this diagnosis. Treat with an alpha-blocker to lower the resistance at the level of the bladder neck.

## HINMAN SYNDROME

**These rare patients represent the extreme end of the dysfunctional voiding spectrum. The syndrome has also been labeled as the nonneurogenic neurogenic bladder.** Hinman noted, in his original description of these patients, the presence of urinary incontinence, fecal soiling, urinary tract infections, and upper tract changes often associated with pyelonephritis; in some cases, renal failure developed. These patients will require a renal bladder ultrasound and a videourodynamics evaluation to ascertain if the bladder is capable of low-pressure storage. Renal function must be assessed. In some instances, a lumbar-sacral MRI and neurologic consultation are warranted to completely exclude any spinal cord lesion. Treatment options for this complex group of patients may include:

1. Timed voiding
2. Antibiotic prophylaxis
3. Biofeedback
4. An assessment of renal function
5. Bowel regimen ranging from MiraLAX to enemas. In the event that these simpler measures fail, more aggressive approaches may be indicated to preserve renal function.

6. Clean intermittent catheterization (CIC): In many of these cases, the use of CIC will actually teach the child how to relax the external sphincter.

In rare instances, patients with Hinman syndrome may become surgical candidates to preserve their renal function.

1. Vesicostomy—if the patient is noncompliant or the social situation is poor and the patient might be lost to follow-up
2. Appendicovesicostomy with or without bladder augmentation
3. ACE procedure for constipation

## NOCTURNAL ENURESIS

This common problem often presents as a seemingly isolated finding. In fact, in taking a careful history, one can often elicit evidence for daytime voiding dysfunction. This is critical because, more often than not, addressing the daytime voiding dysfunction will result in nighttime dryness because the child is actually going to bed with an empty bladder.

### Additional Background

1. **Twenty percent of all 5-year-olds wet the bed.**
2. **This drops by 50% each year. By about age 10, 1% are still experiencing some degree of enuresis.**
3. In a Swedish study, 90% of all neonates would awaken in the minute prior to urination, but 10% slept right on through their voiding. These investigators will ultimately tell us whether these 10% of neonates are the ones presenting at age 5 and beyond with persisting enuresis.
4. Consider the possibility of upper airway obstruction and sleep apnea; these patients need a sleep study and an ear-nose-and-throat (ENT) evaluation.
5. Consider the degree of thirst. Most children with enuresis will not get up to drink at night. If this is happening frequently, consider the possibility of diabetes insipidus (DI).
6. Measure the specific gravity (cheaply done via dipstick) and/or check an osmolality on the first morning urine if you suspect DI.

### Treatments for This Condition

1. Triple void during the hour before bedtime.
2. Aim to consume two thirds of water and fluid intake before noon time.

3. Alarm: This simple electrical circuit is placed in the pajamas and makes a buzzing sound if the contact is established by fluid.
4. Alarms work in 80% of cases after 3 months of work.
5. If the child sleeps through the alarm, the parent must awaken and arouse the child to void. Otherwise, the approach will fail.
6. Alarms work best in cases in which the child is a lighter sleeper.
7. Alarms function as a biofeedback tool. The child learns to associate the sensation of a full bladder during sleep with the need to arouse and then void.
8. Waking the child at set hours during the night to void is not the same as using an alarm because the bladder may not be full at the time the child is awakened.

### Pharmacologic Options for Enuresis

1. DDAVP—nasal spray (rarely used today) or tablet (0.2 mg tablets)
   a. One to three tablets at bedtime
2. Imipramine—25 to 75 mg orally at bedtime (PO QHS)
   a. Rarely used today

## ANTICHOLINERGIC THERAPY IN PEDIATRIC VOIDING DYSFUNCTION

The purpose of anticholinergic therapy is to enhance bladder capacity by eliminating the presence of uninhibited bladder contractions. Most children with dysfunctional voiding have excellent bladder capacity, and thus **anticholinergic therapy is rarely indicated in this population.** On occasion, we will identify children with severe urgency and frequency for whom a trial of oxybutynin (Ditropan) is indicated; however, this is a small number of patients. In these instances, empiric therapy is reasonable, although some might advocate urodynamic or videourodynamic studies prior to such therapy. **There are pediatric patients with overactive bladder who fail anticholinergic therapy who on vidoeurodynamic studies demonstrate unhibited bladder contractions. These highly selected patients may respond to submucosal injections of Botox with an increase in bladder capacity and a drop in their urinary frequency and symptom scores.**

### VOIDING DYSFUNCTION AND VESICOURETERAL REFLUX

Many patients with vesicoureteral reflux will prove to have significant dysfunctional voiding.

1. Treating the dysfunctional voiding is also treating the reflux. Patients with dysfunctional voiding and reflux have a better prognosis for spontaneous resolution than those with voiding dysfunction on a grade for grade basis.
2. Open reimplantation in the face of dysfunctional voiding has a higher complication rate and is to be avoided.

## Diabetes Insipidus

Rarely patients with DI will present to a urologist with voiding dysfunction. These patients have the following characteristics:

1. Thirsty
2. Crave cold water
3. Wake up at night to drink
4. Polyuric
5. Fabulous flow rates

In this setting, the following studies are indicated:

1. First morning urine for specific gravity
2. Water deprivation study with serum and urine osmolarities
3. Treated by endocrinologists with DDAVP

### CLINICAL PEARLS

1. In young females, suspect an ectopic ureter as a possible anatomic cause of severe and continuous urinary incontinence.
2. Constipation is often seen in patients with voiding dysfunction, and treating the constipation often cures the voiding symptoms.
3. A patient who is voiding normally should be able to converse with ease.
4. A thin and weak yet steady stream with the patient unable to converse while applying a Valsalva maneuver would be indicative of a possible stricture.
5. A staccato stream with a start-and-stop pattern would be indicative of striated detrusor sphincter dyssynergia.
6. Cystometry and videourodynamics are rarely indicated in the assessment of pediatric voiding dysfunction.
7. In children with nocturnal enuresis, consider the possibility of upper airway obstruction and sleep apnea; these patients need a sleep study and ear-nose-and-throat (ENT) evaluation.

## DIFFERENTIAL DIAGNOSIS

1. Urinary tract infection
2. Infrequent voider
3. Constipation
4. Striated sphincter dysinergia
5. Internal sphincter dysinergia
6. Hinman syndrome
7. Nocturnal enuresis
8. Diabetes insipidus

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What is the embryologic explanation for the clinical association of constipation and voiding dysfunction?*
2. *What is the embryologic basis for why an ectopic ureter may lead to urinary incontinence only in females?*
3. *Can you explain the difference between striated external sphincter dyssynergia and internal sphincter dyssynergia? How do the pharmacologic treatments for these two conditions differ?*
4. *Can you explain the rationale for use of biofeedback therapy for voiding dysfunction that is based on external sphincteric dyssynergia?*
5. *An 8-year-old child presents for evaluation of persistent urinary incontinence, and during the course of the history, it is revealed that the mother has been an insulin-dependent diabetic for 25 years. What diagnosis must you suspect is present in this child that might account for the urinary incontinence?*

## SUGGESTED READINGS

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# CHAPTER 30

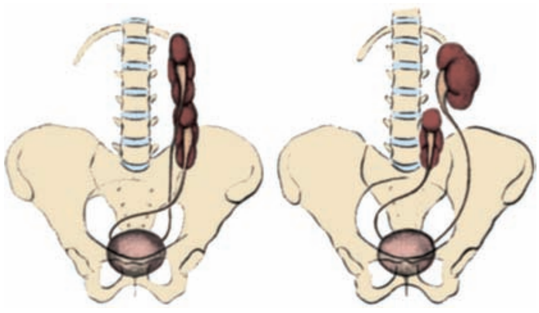
# Congenital Anomalies

Pasquale Casale, MD • Douglas A. Canning, MD

## Upper Urinary Tract

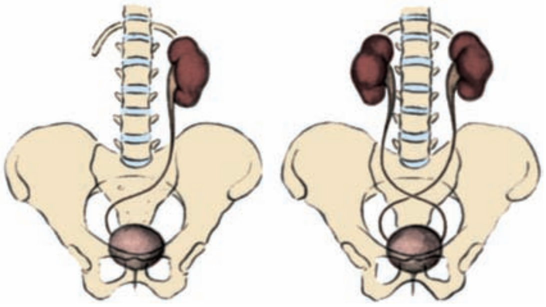
### ABNORMALITIES OF THE KIDNEY POSITION AND NUMBER

1. Simple ectopia
    a. Incidence is approximately 1 per 900 (autopsy) (pelvic, 1 per 3000; solitary, 1 per 22,000; bilateral, 10%). Left side is favored.
    b. Associated findings include small size with persistent fetal lobations, anterior or horizontal pelvis, anomalous vasculature, contralateral agenesis, hydronephrosis (50%), vesicoureteral reflux (30%), müllerian anomalies in 20% to 60% of females; undescended testes, hypospadias, urethral duplication in 10% to 20% of males; skeletal and cardiac anomalies in 20%.
    c. Adrenal gland in normal location
    d. Only workup, ultrasound, voiding cystourethrography (in past routine, now more selective, and only in those with urinary tract infection (UTI))
2. Thoracic ectopia
    a. Comprises less than 5% of ectopic kidneys (1:13,000)
    b. Origin is delayed closure of diaphragmatic angle versus "overshoot" of renal ascent.
    c. **Adrenal is usually in normal location.**
    d. Diagnosis usually is made on plain chest radiograph.
    e. No treatment is needed.
3. Crossed ectopia and fusion (Bauer) (Figures 30-1 and 30-2)
    a. Incidence is 1 per 1000 to 1 per 2000; 90% crossed with fusion; 2:1 male, 3:1 left crossed; 24 cases solitary, five cases bilateral reported to date.
    b. Origin is from abnormal migration of ureteral bud or rotation of caudal end of fetus at the time of bud formation.



Crossed renal ectopia with fusion
A

Crossed renal ectopia without fusion
B



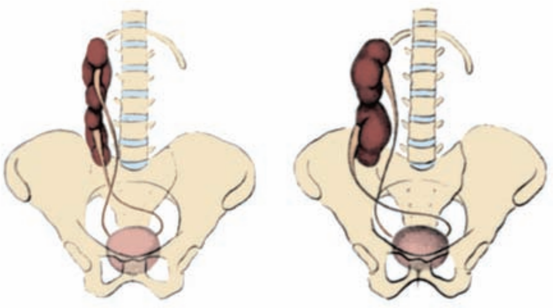
Solitary crossed renal ectopia
C

Bilaterally crossed renal ectopia
D

FIGURE 30-1 **A** to **D, Four types of crossed renal ectopia.** (From Shapiro E, Bauer SB, Chow JS: Anomalies of the upper urinary tract. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

c. Associated findings include multiple or anomalous vessels arising from the ipsilateral side of the aorta and VUR; with solitary crossed kidney only; genital, skeletal, and hindgut anomalies in 20% to 50%. Risk of **ureteropelvic (UPJ) obstruction (30%), VUR (15%) or cystic dysplasia also exists.**

d. Diagnosis is with ultrasound, renal scanning, or magnetic resonance urography (MRU).

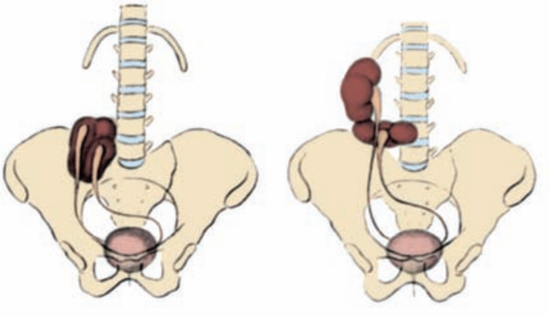


Unilateral fused kidney
(inferior ectopia)

A

Sigmoid or
S-shaped kidney

B

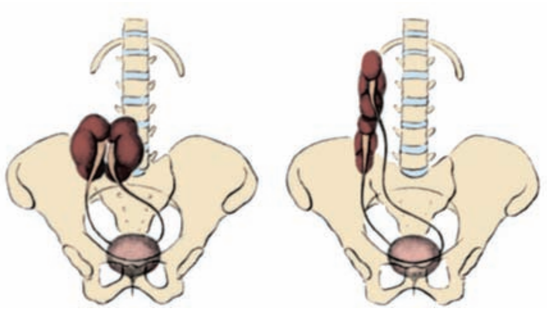


Lump kidney

C

L-shaped kidney

D



Disc kidney

E

Unilateral fused kidney
(superior ectopia)

F

FIGURE 30-2 **A to F, Six forms of crossed renal ectopia with fusion.** (From Shapiro E, Bauer SB, Chow JS: Anomalies of the upper urinary tract. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

4. Horseshoe kidney
    a. Incidence is 1 per 400 or 0.25%; 2:1 males. It is the most common fusion anomaly.
    b. Origin is fusion of lower poles before or during rotation (4½ to 6 weeks gestation) (Figure 30-3).
    c. Associated findings include anomalous vessels; isthmus between or behind great vessels hindered by the inferior mesenteric artery; skeletal, cardiovascular, and central nervous system (**CNS**) **anomalies (33%); hypospadias and cryptorchidism (4%), bicornuate uterus (7%), UTI (13%); duplex ureters (10%), stones (17%); 20% of trisomy 18 and 60% of Turner patients have horseshoe kidney.**
    d. Excluding other anomalies, survival is not affected.
    e. Stones; infection may result from stasis; rarely is true obstruction present (see ureteropelvic junction obstruction [UPJO]).
    f. Most are asymptomatic despite associated anomalies.
5. Bilateral renal agenesis
    a. Incidence is 1 per 4800 births or 1 per 400 newborn autopsies (75% are male) and typically lethal.
    b. Origin is either ureteral bud failure or absence of the nephrogenic ridge.
    c. **Associated findings include absent renal arteries, complete ureteral atresia in 50%, bladder atresia in 50%, Potter syndrome; also low birth weight, oligohydramnios, pulmonary hypoplasia, bowed limbs. Testes are undescended in 45%.**
    d. Several genes, including PAX2/8, Gata3, and Lim1, play a critical role.
6. Unilateral renal agenesis
    a. Incidence is 1 per 1100 in autopsy series, 1 per 1500 in radiographic series, 2:1 male, left kidney is more often involved than right kidney.
    b. Origin is probably ureteral bud failure; there is a familial trend.
    c. Associated findings include absent ureter with hemitrigone (50%), adrenal agenesis (10%), genital anomalies (20% to 40% in both sexes).
        1) **Müllerian anomalies in females include uterovaginal atresia** (Mayer-Rokitansky-Küster-Hauser syndrome), uterus didelphys, and vaginal agenesis (present in 25% to 33% of women).

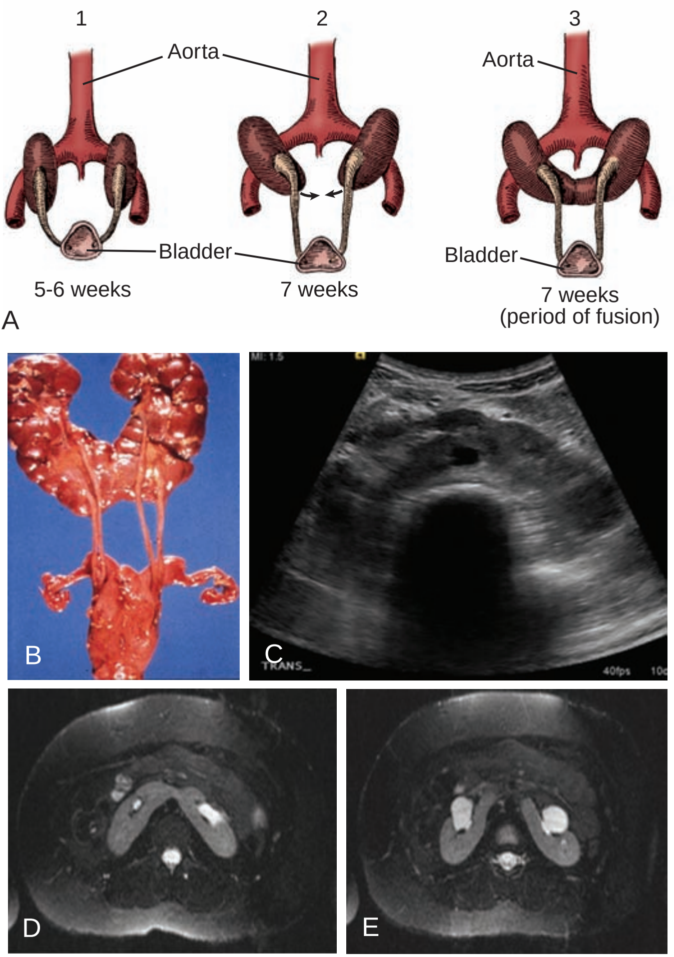


FIGURE 30-3 **A,** Embryogenesis of horseshoe kidney. The lower poles of the two kidneys touch and fuse as they cross the iliac arteries. Ascent is stopped when the fused kidneys reach the junction of the aorta and inferior mesenteric artery. **B,** Postmortem specimen showing horseshoe kidney with bilateral duplicated ureters. **C,** Ultrasonogram of horseshoe kidney at the level of the isthmus. **D,** Magnetic resonance urogram (MRU) shows axial T2 fat-saturated image at the level of the isthmus. **E,** Axial T2 fat-saturated image demonstrates extrarenal pelvis.

(*Continued*)

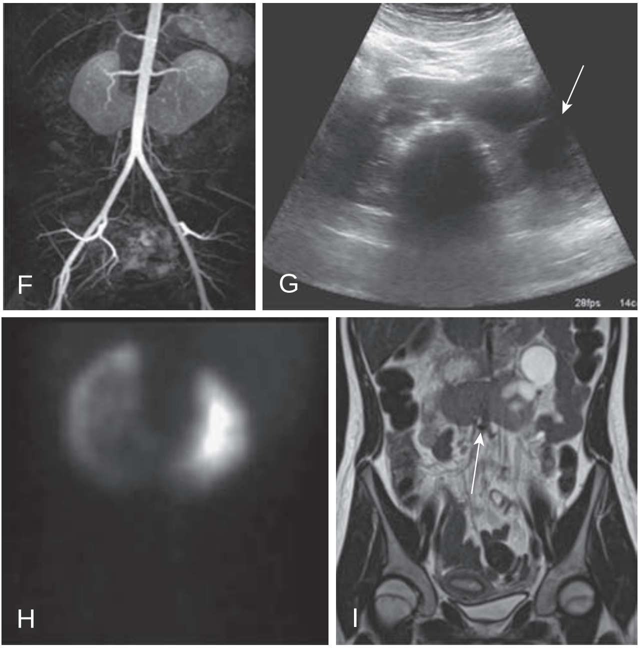


FIGURE 30-3, cont'd **F,** Angiographic sequence shows variable blood supply to the kidney. **G,** Transverse ultrasonogram of 14-year-old girl with left flank pain found to have marked left hydronephrosis in a horseshoe kidney *(arrow)*. **H,** MAG3 scan demonstrates left ureteropelvic junction obstruction (UPJO). **I,** Coronal T2 images of MRU show the isthmus *(arrow)* and severe left hydronephrosis. (**A** from Benjamin JA, Schullian DM: Observation on fused kidneys with horseshoe configuration: The contribution of Leonardo Botallo [1564]. *J Hist Med Allied Sci* 5:315–326, 1950. after Gutierrez, 1931; **B** from Weiss, MA, Mills, SE: *Atlas of genitourinary tract disorders*, Philadelphia, 1988, JB Lippincott. Reprinted in Shapiro E, Bauer SB, Chow JS: *Anomalies of the upper urinary tract.* In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

  2) **In males, the wolffian structures distal to the epididymal head are absent in 50%, including the body and tail of epididymis, vas, and seminal vesicles.**
  3) Cardiac (30%), gastrointestinal (GI) anomalies (25%), and skeletal (15%) are also present.

d. If the single kidney is normal, no special precautions are required, and survival is not affected; management is focused on the genital, cardiac, GI, and skeletal abnormalities.

7. Supernumerary kidney (Figure 30-4)
   a. Incidence is unknown.
   b. Origin is a combined defect of ureteral bud and metanephros.
   c. Associated findings are hydronephrosis (50%), common ureter (40%), duplex ureter (40%), and ectopic ureter or one ending in the pelvis of the ipsilateral kidney (20%).

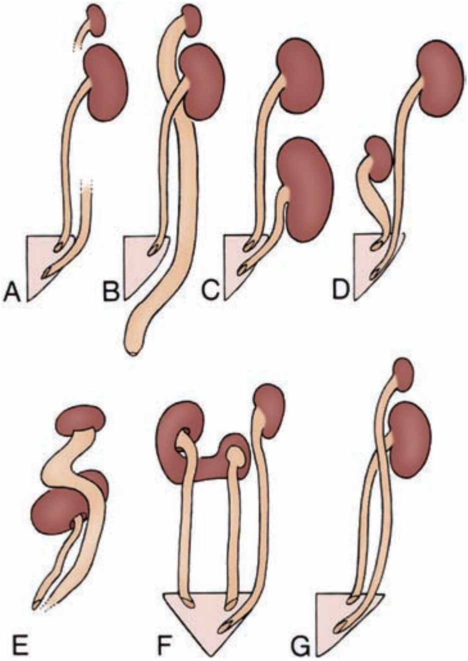


FIGURE 30-4 Rotation of the kidney during its ascent from the pelvis. The left kidney with its renal artery and the aorta are viewed in transverse section to show normal and abnormal rotation during its ascent to the adult site. **A,** Primitive embryonic position; hilus faces ventrad (anterior). **B,** Normal adult position; hilus faces mediad. **C,** Incomplete rotation. **D,** Hyperrotation; hilus faces dorsad (posterior). **E,** Hyperrotation; hilus faces laterad. **F,** Reverse rotation; hilus faces laterad. (**A** from Shapiro E, Bauer SB, Chow JS: Anomalies of the upper urinary tract. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders. **B** from Skandalakis JE, Gray SW: Embryology for surgeons: the embryological basis for the treatment of congenital defects, Philadelphia, 1972, WB Saunders.)

## CYSTIC ABNORMALITIES OF THE KIDNEYS (TABLE 30-1)

1. Autosomal dominant polycystic kidney disease
   a. **Chromosome 16 and chromosome 4.** Two phenotypes: PK1 is more rapidly progressive, and 85% presents in fourth or fifth decade; PK2 (15%) presents in eighth decade.
   b. Autosomal dominant transmission
   c. Adult type is the most common cystic disease in humans, with an incidence of 1 per 1250 live births, and accounts for 10% of all end-stage renal disease (ESRD).
   d. It usually presents between 30 and 50 years of age with pain, hematuria, and progressive renal insufficiency, but it is also seen in children. It rarely present in newborns.
   e. Intravenous urography (IVU) reveals irregular renal enlargement with calyceal distortion; ultrasound shows multiple cysts of variable sizes.
   f. **Associated findings are liver cysts without functional impairment in one third of patients and berry aneurysms (aneurisms of the circle of Willis) in 10% to 40%, also cysts of pancreas, spleen, lungs, colonic diverticula, aortic aneurysms and mitral valve prolapse.**
   g. Complications include uremia, hypertension, myocardial infarction, and intracranial hemorrhage (9%).
   h. Management involves control of blood pressure (BP) and urinary infection, relief of cardiac failure, and eventually dialysis or transplantation. Some of these patients encounter issues with pain typically from renal capsular stretching by the cysts.
   i. Pathology: Rounded or irregular cysts are located in all parts of the nephron.
2. Autosomal recessive polycystic kidney disease
   a. Chromosome 6, autosomal recessive
   b. Infantile type is rare (1 per 10,000 to 50,000 live births) and usually presents with bilateral flank masses in infancy, but it can present in childhood with renal or hepatic insufficiency. Historically mortality is 50%.
   c. IVU shows huge (12 to 16 times normal) kidneys with a pronouncedly delayed nephrogram and a characteristic, streaked appearance (“sunburst” pattern).

### TABLE 30-1 **Characteristics of Major Inheritable and Noninheritable Cystic Kidney Diseases**

*Inheritable*

| Disease Entity | Chromosomal Defect | Renal Findings | Extrarenal Manifestations |
|---|---|---|---|
| Autosomal recessive polycystic kidney disease (ARPKD) | Chromosome 6 | In newborn, usually large, homogeneous, echogenic kidneys | Congenital hepatic fibrosis; biliary dysgenesis |
| Autosomal dominant polycystic kidney disease (ADPKD) | *PKD1:* chromosome 16<br>*PKD2:* chromosome 4<br>*PKD3;* not mapped | Renal cysts scattered throughout parenchyma; large kidneys | Diverticulitis; liver, spleen, pancreatic cysts; mitral valve prolapse; intracranial (berry) aneurysms |
| Juvenile nephronophthisis/medullary cystic disease complex | Chromosome 2; not mapped | Cysts of corticomedullary junction; develop after onset of renal failure; always thickened tubular basement membrane | Retinitis pigmentosa (16%; also known as Senior-Loken syndrome); rarely skeletal abnormalities, hepatic fibrosis, Bardet-Biedl syndrome, ocular motor apraxia, and other neurologic defects |
| Juvenile nephronophthisis (autosomal recessive) | | | |
| Medullary cystic disease (autosomal dominant) | | Cysts of corticomedullary junction; develop before onset of renal failure; tubular basement membrane may NOT be thickened | None |
| Tuberous sclerosis (autosomal dominant) | *TSC1:* chromosome 9<br>*TSC2:* chromosome 16 | Cysts and angiomyolipomas throughout kidney; cysts even present in utero; 3% incidence of RCC | Adenoma sebaceum; epilepsy; mental retardation; cranial tumors |

|  |  |  |  |
|---|---|---|---|
| von Hippel-Lindau disease (autosomal dominant) | Chromosome 3 | Cysts, adenomas, and clear cell RCC (35%-38% of cases) | Cerebellar hemangioblastomas; retinal angiomas; pheochromocytomas; cysts of pancreas and epididymis |

*Noninheritable*

| Disease Entity | Renal Findings | Extrarenal Manifestations |
|---|---|---|
| Multicystic dysplastic kidney | Renal maldevelopment with diffuse cysts and remnants of early metanephros; minimal, if any, nephron development; most frequent renal cystic disease in newborns | Unusual |
| Benign multilocular cyst | Benign cystic neoplasm of the kidney; remainder of kidney has normal nephrons that may be compromised by growing mass; present more often in males when less than 4 years of age and females when greater than 30 years of age | None |
| Simple cysts | Single or multiple cysts; normal nephrons throughout kidney; very common in normal kidneys with increasing age | None |
| Medullary sponge kidney | Ectatic collecting ducts; nephrons usually normal | None |
| Acquired renal cystic disease | Diffuse cysts; adenomas; occasionally RCC; increases with duration of ESRD | None |

*ESRD, End-stage renal disease; RCC, renal cell carcinoma.*

*(From Pope JC IV: Renal dysgenesis and cystic disease of the kidney. In Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 10, Philadelphia, 2012, Saunders.*

   d. It may be distinguished from hydronephrosis, renal tumor, and renal vein thrombosis by IVU and ultrasound (bright echoes on ultrasound).
   e. Associated findings are congenital hepatic (periportal) fibrosis (in all cases) and dilation of bile ducts with the degree of hepatic insufficiency varying inversely with the severity of renal disease and directly with the age of presentation; cysts elsewhere are uncommon.
   f. Complications are renal and hepatic failure, hypertension, and respiratory compromise in the newborn; patients usually die within the first 2 months of life.
   g. Although respiratory support, BP control, and dialysis can improve survival, patients will ultimately develop cirrhosis with all of the associated complications.
   h. Pathology is fusiform dilation of collecting ducts and tubules, resulting in small subcapsular cysts.
3. Medullary sponge kidney (tubular ectasia) is an adult disease pathologically characterized by enlarged tortuous collecting ducts and occasional tiny cysts in the pyramids (75% bilateral; incidence is 1 per 20,000).
   a. Diagnosis: IVU shows collections of contrast adjacent to the calyces (“bristles on a brush” also called “blushing”) often with calcifications in the medulla.
   b. Complications: infection, stones, distal renal tubular acidosis, and hematuria.
   c. Medical management of calculi and infections is often required.
   d. One third of patients with hypercalcemia.
4. Medullary cystic disease (juvenile nephronophthisis) refers to a group of disorders with various genetic patterns characterized pathologically by bilateral small kidneys, attenuated cortex, atrophic and dilated tubules, medullary cysts, and some interstitial fibrosis.
   a. Patients progress to ESRD by about age 20; the juvenile form is responsible for 20% of childhood renal failure deaths.
   b. Medical management of renal failure can delay the need for transplant.
   c. Polydipsia and polyuria are in 80%; retinitis pigmentosa is in 16%.

5. **Unilateral multicystic dysplastic kidney is the most common cystic disease of the newborn** (one in 1000 to 4000 live births) and the second most common abdominal mass in infants after hydronephrosis, including UPJO.
   a. The left kidney is more commonly involved, but there is no sex predilection or familial tendency.
   b. Origin is either (1) ischemic, from failure of the normal shift of vasculature as the kidney migrates, producing also the associated atretic ureter, or (2) failure of the ureteral bud to stimulate metanephric blastoma, or (3) representative of the extreme form of UPJO with atresia of the ureter early in development.
   c. Contralateral renal abnormalities are most common when the multicystic kidney is small and/or the ureteral atresia is low. VUR may be present in up to 20% of cases, but this may not be clinically apparent.
   d. Ultrasound is the most diagnostic study (multiple hypoechoic areas of various sizes without connections or dominant medial cyst and without identifiable parenchyma) because VUR commonly is present, Every child with a history of UTI should undergo voiding cystoscopy (VCUG). If there is less than confirmatory imaging on ultrasound, renal scintigraphy (DMSA or MAG3) will confirm the diagnosis with no flow or function present.
   e. Histopathology includes atretic artery, cysts, some solid central stroma, low cuboidal epithelium, some primitive nephrogenic structures, and occasionally immature glomeruli.
   f. **In most, the cystic kidney usually does not enlarge as the child grows and thus becomes relatively less conspicuous. Most can be followed. Reports of hypertension are rare. Malignant transformation, previously feared, is exceedingly rare and not thought to be a clinical threat and is no higher risk than in normal kidneys Removal of the cystic kidney is now only recommended in those in whom the kidney has enlarged over time.**

## COLLECTING SYSTEM ABNORMALITIES

1. Calyceal diverticulum occurs in 4.5 per 1000 urograms.
   a. Origin is failure of degeneration of third- and fourth-order branches of ureteral bud, leaving a pocket lined with transitional epithelium connected to the collecting system near the calyceal fornix.

   b. In approximately one third of patients, stones will form; some will become sites of persistent infection because of stasis; the rest remain asymptomatic.
   c. Treatment involves removal of stones, drainage of purulence, and marsupialization to the renal surface with closure of the collecting system and cauterization of the epithelium.
2. Hydrocalycosis is a rare lesion involving vascular compression, cicatrization, or achalasia of the infundibulum; it rarely requires any intervention.
3. Megacalycosis is a rare lesion involving all of one or both kidneys with dilated unobstructed calyces usually numbering more than 25 per kidney (normally 8 to 10 calyces per kidney). It may be confused radiographically with obstructive uropathy.
   a. Results from a combination of faulty ureteral bud division, hypoplasia of juxtamedullary glomeruli, and maldevelopment of calyceal musculature
   b. Males 6:1 over females, only in Caucasians; X-linked recessive gene
   c. May be associated with stones or infection but in itself causes no deterioration of renal function
4. Infundibulopelvic stenosis may involve part or all of one or both kidneys.
   a. The calyces become quite large, but usually no progressive functional deterioration occurs. Pain is difficult to manage when present.
   b. May be associated with dysplasia and lower tract anomalies (e.g., urethral valves)
   c. Commonly associated with VUR
5. UPJO is the usual cause of the most common abdominal mass in children (hydronephrosis).
   a. There is a 2:1 male predominance in children and left-sided predominance in all ages.
   b. **Several possible causes, including segmental muscular attenuation or malorientation, true stenosis, angulation, and extrinsic compression** (Figures 30-5 and 30-6). Crossing lower-pole vessels are present in approximately 20% to 30% of cases, but an intrinsic lesion (either noncompliant or nonconducting) is common. Lower-pole UPJO can occur in duplex ureters. Rarely secondary UPJO can follow severe VUR. In these cases, correction of the VUR may result in better upper drainage.

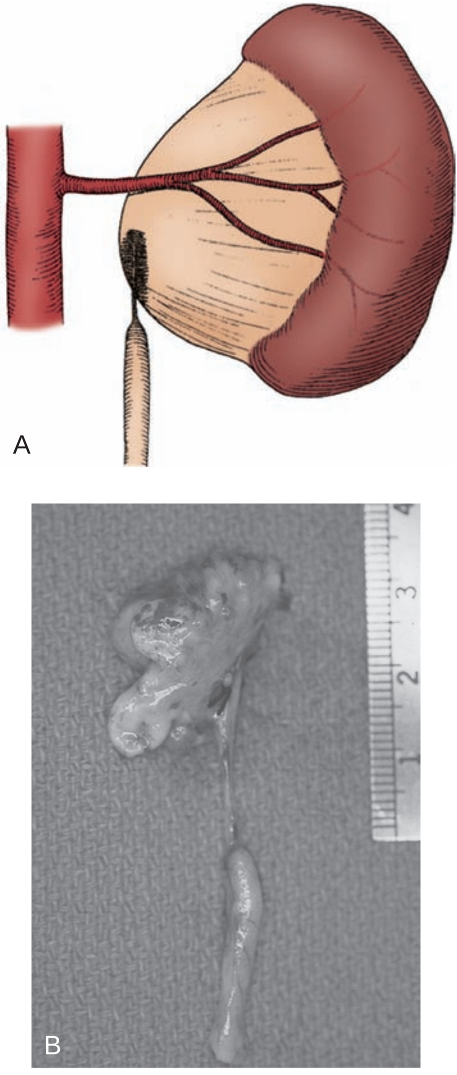


FIGURE 30-5 **A,** Intrinsic narrowing of upper ureter contributing to ureteropelvic junction obstruction (UPJO). **B,** Surgical specimen of nonfunctioning kidney with significant proximal ureteral narrowing. (From Carr MC, Casale P: Anomalies and surgery of the ureter in children. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

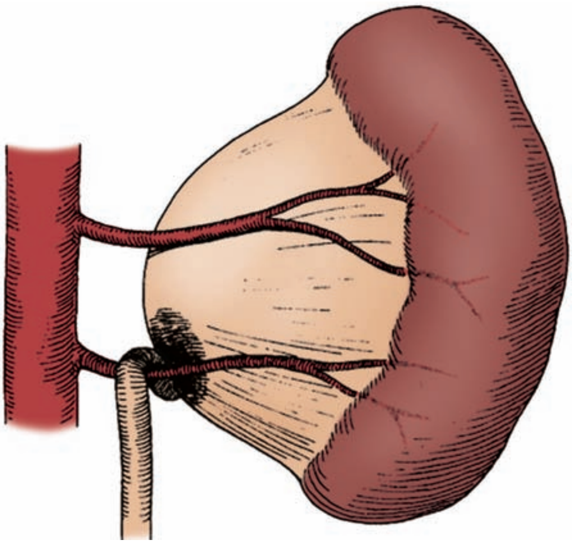


FIGURE 30-6 A lower pole crossing vessel contributes to significant kinking at the ureteropelvic junction (UPJ) and resultant intermittent obstruction. Often, when the ureter is mobilized, no evidence of intrinsic narrowing is found. Insertional anomaly and peripelvic fibrosis may also be present as secondary obstructive factors. (From Carr MC, Casale P: Anomalies and surgery of the ureter in children. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

c. **Associated findings include reflux (5% to 10%), contralateral agenesis (5%), and contralateral UPJO (10%); rarely dysplasia, multicystic kidney, or other urologic anomaly.**

d. Many infants with UPJO will be identified in utero with routine prenatal screening ultrasounds. For the few who develop symptoms, symptoms and signs include episodic flank pain and/or mass, hematuria, infection, nausea and vomiting, and sometimes uremia. In infants, the flank mass may be the only sign, whereas the older child will exhibit any of the others; very often GI distress and poorly localized upper abdominal pain are the only symptoms.

e. Radiologic findings are delayed excretion on the affected side with variable dilation of pelvis and calyces, or on ultrasound, multiple interconnected hypoechoic areas with dominant medial hypoechogenicity and identifiable cortical rim. There is usually some measurable function on renal scan. When function is good, the drainage is delayed even in the face of furosemide (Lasix) administration beyond 20 minutes.

f. Prompt surgical repair is done by excision of the narrow segment and a spatulated anastomosis of the ureter to the tailored renal pelvis for symptomatic cases. If an associated obstructing lower-pole vessel is present, the vessel is placed posterior to the anastomosis (Figure 30-7). Most are diagnosed antenatally and can be followed with serial renal scan and ultrasound.

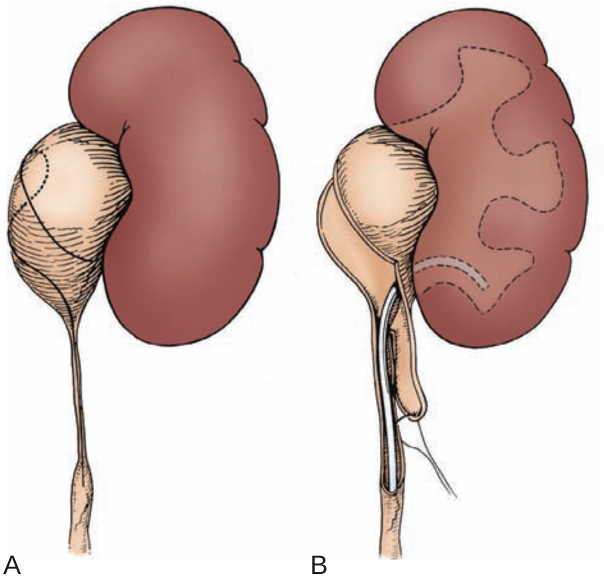


FIGURE 30-7 **A,** The intubated ureterotomy may be of value when a ureteropelvic junction obstruction is associated with extremely long or multiple ureteral strictures. A spiral flap is outlined and developed as described in. The ureterotomy incision will be carried completely through the long, strictured area or through each of the multiple areas of stricture. **B,** The flap is developed, taking care to use minimal dissection of the ureter to preserve its blood supply. In contrast to uncomplicated repairs, nephrostomy tube drainage is used routinely. A self-retaining, soft, inert, internal ureteral stent is placed and positioned proximally in the renal pelvis or lower infundibulum and distally in the bladder. The apex of the flap is brought as far down as possible over the stent on the ureterotomy. The flap is closed with interrupted or running absorbable sutures.

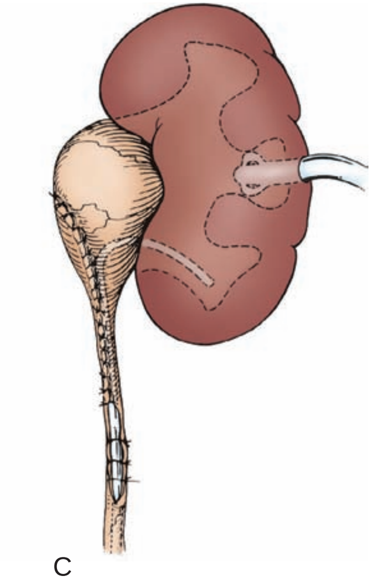


**FIGURE 30-7, cont'd C,** **The distal aspect of the ureterotomy is left open to heal secondarily by ureteral regeneration. A few fine absorbable sutures may be placed loosely to keep the sides of the ureter in apposition to the stent.** (From Carr MC, Casale P: Anomalies and surgery of the ureter in children. In Wein AJ, Kavoussi LR, Novick AC, et al, editors: *Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders.)

  g. Follow-up consists of ultrasound at 1 month, renal scan at 3 months, and ultrasound at 1 year postoperatively in most cases.

## URETERAL ANOMALIES

1. Duplication of ureter occurs in 1 per 125 autopsies; 1.6:1 female, 85% unilateral.
   a. Autosomal dominant with incomplete penetrance
   b. Most cases seem to arise from two ureteral buds meeting the metanephros. Another cause is a bud that bifurcates immediately after arising before meeting the metanephros.
   c. Associated with reflux (42%), renal scarring and dilation (29%), ectopic insertion (3%), large kidneys with excess calyces, dysplasia/hypoplasia, infection, and ureteroceles

   d. Duplication itself is of no clinical significance, but the associated anomalies may require intervention (ureterocele, ectopia).
2. Atresia is usually associated with a multicystic dysplastic kidney; distal segment atresia is often associated with contralateral hydronephrosis or dysplasia (50%).
3. Megaureter has a 3:1 male and 3:1 left-sided predominance; the term is used loosely to describe any dilated ureter, but there are three distinct types. Most cases of megaureter, which is similar to UPJO, are now identified on antenatal ultrasound.
   a. Refluxing megaureter develops because of the reflux, although some cases have an abnormal distal segment and some element of obstruction.
   b. A widened ureteral bud gives rise to a ureter dilated down to the orifice, which is in the normal position, and there is no obstruction (nonreflux, unobstructed type).
   c. The primary obstructed type is the most common and results from a stenotic or aperistaltic distal short segment; the orifice is in the normal position.
   d. The refluxing type, with its laterally ectopic orifice, may be associated with a dysplastic kidney, one scarred by infection, or both; the other types drain normal or hydronephrotic kidneys.
   e. The ultrasound will show moderate to severe hydronephrosis and proportionately greater ureteral dilation; VCUG will diagnose the reflux type; a Lasix renogram would distinguish obstructed from unobstructed types.
   f. There are mild primary obstructed megaureters with only a spindle-shape dilation of the distal ureter and normal (sharp) calyces; these require no treatment.
   g. Surgical correction is needed for some obstructed and refluxing megaureters. Refluxing megaureters more commonly require tailoring than obstructed ones, which tend to decrease in caliber after excision of the aperistaltic distal segment.
   h. Follow-up includes ultrasound at 1 month and renal scan at 3 months. An ultrasound is done 1 year postoperatively.
4. VUR occurs in approximately 1 per 1000 in the general population but is 8 to 40 times more frequent in affected families; it can be found in 50% of infants and 30% of children with a UTI. It may occur in as many as 17% of children without a UTI.

a. **Primary VUR may occur because the ureteral bud arises ectopically leading to a laterally placed orifice and short submucosal tunnel or because the development of the intrinsic smooth muscle of the distal ureteral segment is delayed or incomplete. Secondary ureteral reflux occurs when high intravesical pressures may cause a marginally competent ureterovesical junction to reflux; evidence is growing that voiding dysfunction in the child may cause or exacerbate reflux.**

b. Duplicated ureters and renal hypodysplasia may be associated with refluxing ureters with laterally ectopic orifices. Infection and renal scarring are prominent findings with all types of refluxing ureters regardless of grade. Voiding dysfunction and urethral obstruction by valves are associated with an acquired form of reflux.

c. **Primary VUR is graded I to V by the International Reflux Study system depending on the degree of dilation** (**Figure 30-8**)**. Scarring is present in greater proportions in children with higher grades of VUR** (**Table 30-2**)**.**

d. **All children with reflux should be placed on prophylactic antibiotics at one fourth the therapeutic dose given once a day.** Trimethoprim-sulfamethoxazole and nitrofurantoin are the most commonly used drugs after 2 months of age. Typically, amoxicillin is used in the newborn

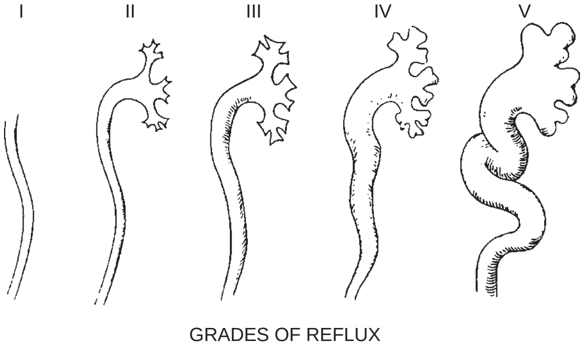


**FIGURE 30-8 International Reflux Study classification of vesicoureteral reflux (VUR).** (From Atala A, Keating MA: Vesicoureteral reflux and megaureter. In Walsh PC, Vaughn ED, Retik AB, et al, editors: *Campbell's Urology,* ed 8, Philadelphia, 2002, Saunders.)

TABLE 30-2 **Congenital Renal Scarring**

| Grade of Vesicoureteral Reflux | Number of Patients Normal | Slight Damage | Severe Damage |
|---|---|---|---|
| 1-3 | 13 (100%) | — | — |
| 4 | 8 (53%) | 5 (34%) | 2 (13%) |
| 5 | 2 (15%) | 5 (38%) | 6 (46%) |

*(Modified from Marra G, Barbieri G, Dell'Agnola CA, et al: Congenital renal damage associated with primary vesicoureteric reflux.* Arch Dis Child Fetal Neonatal Ed *70:F147, 1994. (table 122-4 from Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology*, ed 10, Philadelphia, 2012, Saunders, p 3280.)*

period until 2 months of age. Children require periodic upper tract radiographic assessment usually with ultrasound and reevaluation of the reflux by VCUG or nuclear VCUG. Some physicians advocate the use of dimercaptosuccinic acid (DMSA) to screen and follow for scarring in patients monitored with VUR because renal scarring is truly the detrimental effect of VUR and pyelonephritis (Table 30-3).

e. Grades 1-3 (minimally dilated) are usually treated medically initially; grades 4-5 usually require surgical correction. Low-volume VUR (grades 1-3) resolves at a rate of 17% per patient-year, whereas grade 4 VUR resolves at a rate of 4% per patient-year.

f. Reimplantation of the refluxing unit by the Cohen technique (transvesical) or through extravesical detrusorrhaphy approaches is the standard open surgical management, with nearly complete success; duplicated ureters are reimplanted in their common distal muscular sheath. Recently subureteric injection and laparoscopic and vesicoscopic approaches have been used with good success in preliminary reports.

g. Breakthrough infections, failure to comply with the antibiotic prophylaxis regimen, persistent reflux into puberty in females, progressive scarring, and worsening renal function are all considerations that favor surgical intervention, but there are no absolute indications for surgery for reflux.

5. The incidence of ureteral ectopia is approximately 1 per 1900; ectopic ureters are duplex in 80% of females, more often single in males; there is a 3:1 female predominance, and approximately 10% are bilateral.

TABLE 30-3 **Treatment Recommendations for Boys and Girls with Primary Vesicoureteral Reflux**[*]

| VUR Grade and Laterality | Clinical Manifestation Age (yr) | Initial (Antibiotic Prophylaxis or Open Surgical Repair) Guideline | Follow-Up[†] (Continued Antibiotic Prophylaxis, Cystography, or Open Surgical Repair) Preferred Option | Reasonable Option | Guideline | Preferred Option | No Consensus[‡] |
|---|---|---|---|---|---|---|---|
| ***For Children without Scarring at Diagnosis*** | | | | | | | |
| 1-2, unilateral or bilateral | < 1 | Prophylaxis | | | | | Boys and girls |
| | 1-5 | Prophylaxis | | | | | Boys and girls |
| | 6-10 | Prophylaxis | | | | | Boys and girls |
| 3-4, unilateral or bilateral | < 1 | Prophylaxis | | | Bilateral: surgery if persistent[§] | Unilateral: surgery if persistent[§] | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 1-5 | Unilateral: prophylaxis | Bilateral: prophylaxis | | | Surgery if persistent[§] |
| | 6-10 | | Unilateral: prophylaxis | Bilateral: prophylaxis | | Surgery if persistent[§] |
| | | | Bilateral: surgery | | | |
| 5, unilateral or bilateral | < 1 | | Prophylaxis | | Surgery if persistent[§] | |
| | 1-5 | | Bilateral: prophylaxis | Bilateral: prophylaxis | Surgery if persistent[§] | |
| | | | Unilateral: prophylaxis | Unilateral: surgery | | |
| | 6-10 | Surgery | | | | |

(*Continued*)

TABLE 30-3 **Treatment Recommendations for Boys and Girls with Primary Vesicoureteral Reflux**—Cont'd

| VUR Grade and Laterality | Clinical Manifestation Age (yr) | Initial (Antibiotic Prophylaxis or Open Surgical Repair) Guideline | Follow-Up[†] (Continued Antibiotic Prophylaxis, Cystography, or Open Surgical Repair) Preferred Option | Reasonable Option | Guideline | Preferred Option | No Consensus[‡] |
|---|---|---|---|---|---|---|---|
| *For Children with Scarring at Diagnosis* | | | | | | | |
| 1-2, unilateral or bilateral | < 1 | Prophylaxis | | | | | Boys and girls |
| | 1-5 | Prophylaxis | | | | | Boys and girls |
| | 6-10 | Prophylaxis | | | | | Boys and girls |
| 3-4, unilateral | < 1 | Prophylaxis | | | Girls: surgery if persistent[§] | Boys: surgery if persistent[§] | |
| | 1-5 | Prophylaxis | | | Girls: surgery if persistent[§] | Boys: surgery if persistent[§] | |
| | 6-10 | | Prophylaxis | | Surgery if persistent[§] | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3-4, bilateral | < 1 | Prophylaxis | | | Surgery if persistent[§] | |
| | 1-5 | | Prophylaxis | Surgery | Surgery if persistent[§] | |
| | 6-10 | Surgery | | | | |
| 5, unilateral or bilateral | < 1 | | Prophylaxis | Surgery | Surgery if persistent[§] | |
| | 1-5 | Bilateral: surgery | Unilateral: surgery | | | Surgery if persistent[§] |
| | 6-10 | Surgery | | | | |

*(From American Urological Association. Report on the management of vesicoureteral reflux in children. Baltimore: American Urological Association, Pediatric Vesicoureteral Reflux Clinical Guidelines Panel; 1997.) (Table 122-6 from Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 10, Philadelphia, 2012, Saunders.)*

*Guidelines: Treatments were selected by eight or all of nine panel members, given the strongest recommendation language.*

*Preferred Options: Treatments were selected by five to seven of nine panel members.*

*Reasonable Alternatives: Treatments were selected by three to four of nine panel members.*

*No Consensus: Treatment was selected by no more than two of nine panel members.*

* Recommendations were derived from a survey of preferred treatment options from 36 clinical categories of children with reflux. The recommendations are classified as follows:

† For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.

‡ No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.

§ See the text regarding the length of time that clinicians should wait before recommending surgery.

a. The cause is a failure of the ureteral bud to separate from the mesonephric duct, probably due to its ectopic origin on the duct.
b. Locations are shown in Figure 30-9.
c. Associated findings

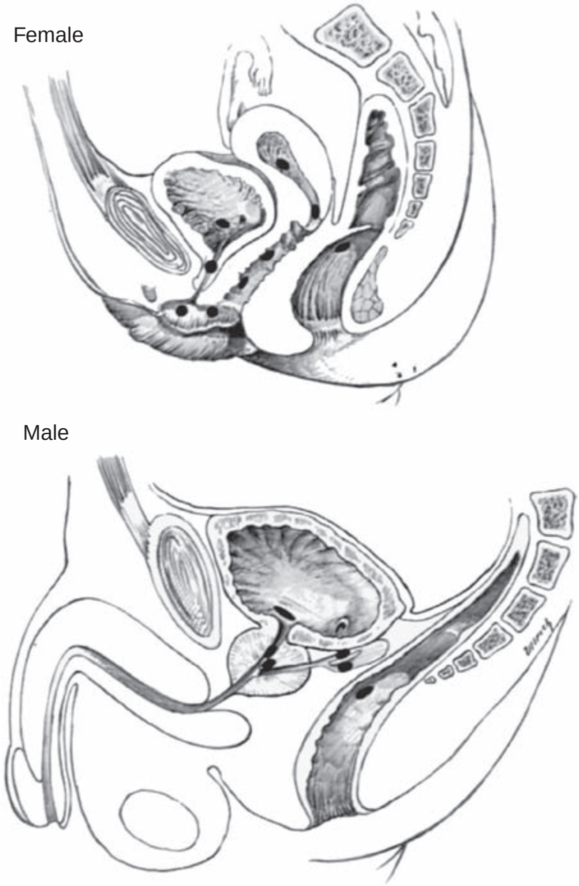


**FIGURE 30-9 Sites of ectopic ureteral orifices in girls and boys.** (From Schlussel R, Retik R: Ectopic ureter, ureterocele, and other anomalies of the ureter. In Walsh PC, Vaughn ED, Retik AB, et al, editors: *Campbell's Urology,* ed 8, Philadelphia, 2002, Saunders, 2002, p 2014.)

        1) **Renal dysplasia correlates with the degree of ectopy.**
        2) **Contralateral duplication accompanies single ectopic ureter in 80%.**
        3) **Incontinence and ureteral obstruction are variable findings; incontinence may be due to an orifice located below the sphincter in females or to failure of bladder neck development.**
            a. Bilateral single ectopic ureters, in which the orifice is distal to the bladder neck, lead to poorly developed bladder and incontinence because of outlet incompetence and failure of bladder cycling.
    d. Management is most often removal of the renal segment and ectopic ureter; rarely the segment may be salvageable by ureteroureterostomy or reimplantation.

6. Ureterocele occurs with a frequency between 1 per 500 and 1 per 4000 in autopsies, accounting for approximately 1% of pediatric urologic admissions and is bilateral in 10% to 15% of cases; females 4:1 over males.
    a. It develops because of a combination of an abnormal ureteral bud with either a stenotic orifice or involvement of the distal ureter in the expansion of the vesicourethral canal. The ureter is duplicated in children (80%), with the ureterocele draining the upper pole ureter. Presence of a simple ureterocele subtending a single ureter is less common in children.
    b. Associated anomalies include contralateral ureteral duplication in 50%; renal segmental dysplasia; renal fusion and ectopia; reflux (50%); and, rarely, incontinence.
    c. Classification is based on location of the orifice and is typically defined as *intravesical* or *ectopic*.
    d. Cecoureterocele, a subclassification of ectopic ureterocele, differs in that a “cecum” extends beyond the orifice down the urethra; it may be associated with poor bladder neck development and incontinence.
    e. Management is varied.
        1) Puncture of the ureterocele as newborn
        2) Upper-pole nephrectomy with decompression of the ureterocele
        3) Upper-pole nephrectomy with decompression of the ureterocele and with lower excision of the ureterocele

with common sheath reimplantation and bladder-neck reconstruction

4) Puncture of the ureterocele as newborn, with delayed excision of ureterocele plus reimplant with bladder neck reconstruction if VUR persists or occurs following puncture of the ureterocele. It appears that whether one takes an approach that favors removal of the upper tract moiety only or puncturing the ureterocele, the development of de novo VUR is relatively the same (10% to 15%).

## Lower Urinary Tract

### EXSTROPHY/EPISPADIAS — SPECTRUM OF ANOMALIES

1. Origin is failure of the cloacal membrane to migrate toward the perineum at 4 weeks gestation, preventing ingrowth of lateral mesoderm and coalescence of genital tubercles.
   a. The most consistent finding is some degree of separation of symphysis pubis.
   b. Epispadias (30%) occurs in about 1 in 100,000 live births. It may be penopubic with incontinence in males (55%), penile (20%) with or without incontinence, or balanitic (5%), or it may occur in females with incontinence (20%). It consists of a dorsal meatus with a distal mucosal groove, flattened glans, or bifid clitoris; in males, there is a variable dorsal chordee with shortening of the corporal bodies in severe forms (penopubic).
   c. Nearly all cases of epispadias require complete disassembly with or without complete separation of the distal urethra from the glans (Mitchell) technique. Most of these boys are treated in the newborn period.
   d. Classic exstrophy (60%) occurs in one per 50,000 births with 3:1 male predominance; the bladder and the urethra are open dorsally, and the penis is short or the clitoris is bifid.
   e. Cloacal exstrophy (10%) results from the condition of failure of the urorectal septum to descend. It occurs approximately in one per 200,000 births, about equally in males and females.

2. Associated findings
    a. In classic exstrophy, because of a shortened inguinal canal, undescended testes and inguinal hernias are common; often the infraumbilical rectus fails to develop; vaginal stenosis and/or bifid uterus may be present; the upper urinary tract is usually normal or may be duplex.
    b. In cloacal exstrophy, there are a vesicointestinal fissure opening into the center of the exstrophied bladder, short blind distal colon, absent or duplicated appendix, and often omphalocele. Two thirds of females have an absent or duplex and stenotic vagina; nearly all have a tethered spinal cord with 50% having myelomeningocele. The penis or clitoris is bifid or may be absent.
3. **Exstrophy may be managed in stages or by primary single repair. A staged closure begins with bladder closure in the newborn period.**
    a. Penile lengthening by freeing corpora from pubic bone attachments and tubularization of the bladder neck is accomplished during the first stage.
    b. In cloacal exstrophy, the omphalocele and vesicoenteric fissure must be dealt with by lateral closure of the bowel end colostomy and omphalocele repair. The bladder halves are approximated in the first stage.
4. The second stage is epispadias repair, in most cases at approximately 1 to 2 years of age.
5. The third stage in those with functioning, sufficiently large bladders is achieving continence by bladder neck tubularization (60% success).
    a. Those who fail this are candidates for augmentation plus intermittent catheterization.
    b. Most cloacal exstrophy patients have undergone early ileal loop diversion, but a few may be reconstructed along the same principles.
6. Second option is complete penile disassembly with bladder closure and bladder neck and epispadias repair all done at a single stage (Mitchell repair). Despite the name, many of these patients require additional procedures to achieve urinary continence.
7. All patients require careful follow-up throughout life with survey of the upper tracts by IVU or ultrasound, monitoring of acid-base balance, renal function tests, and supportive counseling.

## URACHUS

Patent urachus and persistence of portions of the urachus as cysts result from failure of fibrosis of the cranial embryonic bladder segment; they are excised when symptomatic. If infected, primary drainage, antibiotic coverage, and secondary resection are appropriate. In a few cases, the urachal segment may undergo malignant transformation (adenocarcinoma).

## POSTERIOR URETHRAL VALVES (TYPE I)

1. The incidence is one per 5000 to 8000 boys; more than 50% are diagnosed in the first year of life, generally with more severe obstructions.
2. Proposed cause is failure of regression of the terminal segment of the mesonephric duct, which is normally represented by the plicae colliculi. Type II valves are unobstructing normal folds in the prostatic urethra and not currently recognized as true valves; type III valves represent either more marked anterior fusion of the valve leaflets or congenital urethral membrane (a separate embryologic entity). Recent observations suggest that types III valves are variations of type I valves.
3. Associated findings
   a. Secondary VUR (40%, approximately one half bilateral) resolves in approximately one third of cases generally within 2 years. Persistent unilateral reflux is usually associated with a nonfunctioning kidney, most commonly the left one.
   b. Severe renal dysplasia is common in those with severe obstruction.
   c. Severe hydroureteronephrosis
   d. Acute renal failure and acidosis in the newborn are obstructive phenomena; chronic renal insufficiency from dysplasia may occur (Table 30-4).
4. Diagnosis
   a. Antenatal diagnosis in most cases
   b. UTI or poor stream in an infant or older child; incontinence occasionally in an older child
   c. A newborn with palpable bladder, kidneys and urinary ascites.
   d. VCUG is the diagnostic study; ultrasonography and renal scan are employed to assess the extent of upper tract damage and postoperative recovery.

TABLE 30-4 **Damage Due to Posterior Urethral Valves**

| Organ | Effect | Natural History |
|---|---|---|
| Lung | Pulmonary hypoplasia | May be fatal in newborns; if infant survives, there are few long-term problems |
| Kidney | | |
| Glomerular injury | | |
| Obstructive uropathy | Reversible renal insufficiency | Usually improves with initial treatment but can recur with bladder dysfunction |
| Dysplasia | Irreversible renal insufficiency | Permanent level of renal damage that limits growth; leads to progressive renal failure and hypertension |
| Tubular injury | Inability to limit sodium and water loss | Progressive with age; nephrogenic diabetes insipidus |
| Bladder | Poor sensation, hypercontractility, low compliance, and eventual myogenic failure all may contribute to incontinence and poor emptying | Bladder problems are lifelong and change with age |
| Ureters | Poor contractility and inability to coapt and transport urine | Most will improve initially but have chronic hydronephrosis |

*(From Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 10, Philadelphia, 2012, Saunders.)*

5. **Management**
   a. **In the sick infant, bladder drainage with a small feeding tube (6F) per the urethra is maintained while acidosis and sepsis are treated; VCUG may be done with this catheter in place.**

   b. **The healthy infant or older child may undergo transurethral incision of valves initially; the sick infant when creatinine stabilizes and sepsis resolves.**
   c. **Cutaneous vesicostomy can be used as a temporizing measure in a very small infant but is rarely required with today's endoscopic equipment.**
   d. Nonfunctioning kidneys with refluxing ureters should be preserved. The ureters may be used as tissue for augmentation of the bladder if needed at the time of renal transplant.
   e. Ureteral tailoring and reimplantation are almost never indicated and are often fraught with failure.
   f. Antibiotic prophylaxis is maintained as long as reflux persists or upper tract emptying is slow (usually through adulthood).
6. Results
   a. **Children whose creatinine levels stabilize below 0.7 mg/dL after relief of obstruction generally do well, whereas those with creatinine levels above 1.0 mg/dL often "outgrow" their renal function by puberty and require transplantation.**
   b. Continence is eventually achieved in virtually all who undergo valve incision. Bladder volume increases. Some children must practice double voiding or intermittent catheterization to ensure complete bladder emptying.

## MEGALOURETHRA

1. This rare lesion is usually associated with prune belly syndrome.
2. Occurs in two types
   a. **Scaphoid type is a deficiency of corpus spongiosum allowing ballooning of the urethra during voiding; it can be repaired with hypospadias techniques.**
   b. **Fusiform type involves deficiency of corpora cavernosa and corpus spongiosum, resulting in an elongated flaccid penis with redundant skin. This form is seen usually in stillborn infants with other cloacal anomalies and is difficult to correct because of the lack of adequate corporal tissue.**

## MISCELLANEOUS

1. An anterior urethral valve or diverticulum is a rare obstructing lesion with a large saccular outpouching and obstructing distal lip of mucosa. The diverticulum is excised with careful attention to prevent the distal flap from obstructing.

2. Enlarged utriculus masculinus is a dilated müllerian remnant, usually asymptomatic and associated with hypospadias or an intersex state; it can be excised retrovesically or transvesically if stasis leads to UTI or the full utricle interferes with bladder emptying. These rarely require surgical intervention.
3. Aphallia and diphallia are exceedingly rare failure of fusion of the genital tubercles or failure of differentiation of the phallic mesenchyme.
4. Micropenis is often associated with CNS lesions or an intersex state; gender conversion, practiced in some cases in the past, is almost never considered currently.

## External Genital Malformations

### HYPOSPADIAS

Hypospadias occurs in 1 in 300 live boys; there is a 14% incidence in siblings and an 8% incidence in offspring.

1. It is caused by failure of the mesodermal urethral folds to converge in midline; chordee results from failure of urethral plate disintegration or fibrosis of inner genital folds (which form the spongiosum and dartos fascia).
2. Associated findings
   a. Blunted human chorionic gonadotropin response to gonadotropin-releasing hormone and low androgen-receptor levels in a few cases
   b. Undescended testes occur in 9.3% (30% with penoscrotal or more proximal meatus). Up to one third of boys with hypospadias and undescended testes have an intersex state, usually genetic mosaicism.
   c. Inguinal hernia in 9%
   d. Upper tract anomalies occur in 46% when associated with imperforate anus, 33% when meningomyelocele is present, 12% to 50% when one other system anomaly is present, 5% with isolated hypospadias (screening intravenous pyelogram [IVP] not needed for simple hypospadias).
3. Classification (simplified) (Figure 30-10)
   a. Hypospadias without chordee (straight erections, meatus between midshaft and corona)
   b. Hypospadias with chordee

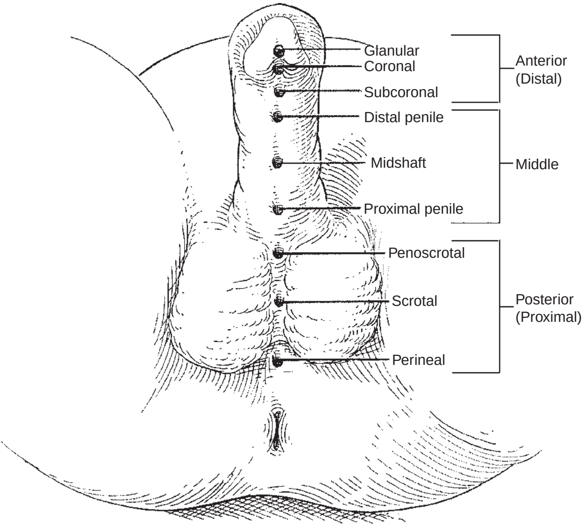


**FIGURE 30-10 Anatomically descriptive levels of hypospadias within the three major categories, based on the level of the meatus following orthoplasty.** (From Retik AB, Borer JG: Hypospadias. In Walsh PC, Vaughn ED, Retik AB, et al, editors: *Campbell's urology,* ed 8, Philadelphia, 2002, Saunders.)

1) Meatus penile or penoscrotal after release of chordee
2) Meatus scrotal or perineal
   c. Chordee with hypospadias
1) With normal urethra
2) With short or hypoplastic urethra
4. Management
   a. One-stage correction between 4 and 12 months of age is preferred.
   b. Glanular hypospadias may be corrected by meatal advancement and glanuloplasty (MAGPI) (Figure 30-11). For coronal repairs, the Snodgrass, tubularized incised plate (TIP) (Figure 30-12), onlay island flap (Figure 30-13) procedures are the most commonly employed, depending on meatal position and surgeon preference.
   c. Penile shaft or more proximal hypospadias may be managed by inner preputial transverse island flap (Figure 30-14).

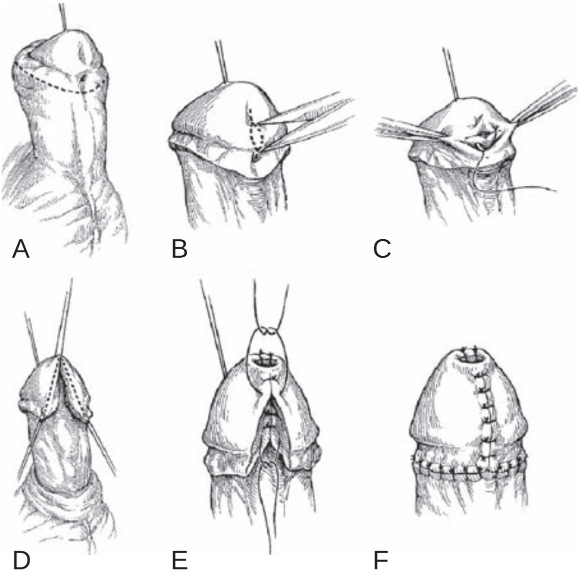


FIGURE 30-11 Meatoplasty and glanuloplasty (MAGPI). **A,** Circumferential subcoronal incision is marked. Longitudinal incision **(B)** and transverse approximation **(C)** (Heineke-Mikulicz procedure) of transverse granular "bridge" in urethral plate. **D,** Ventral edge of meatus is pulled distally, and medial glands "trimming" incisions are marked. **E,** Deep suture approximation of the glands. **F,** Superficial approximation of the glans and skin. (From Duckett JW: Hypospadias. In Walsh PC, Retik AB, Vaughan ED Jr, et al, editors: *Campbell's urology,* ed 7, Philadelphia, 1998, Saunders.)

d. Severe penoscrotal hypospadias may require combined island flap and primary (Duplay) closure of the proximal urethra and may need secondary scrotoplasty to improve the cosmetic result. In many cases two-stage repairs are required in severe hypospadias.
e. Degloving the penis and mobilizing the urethra may treat skin chordee without urethral involvement.
f. Chordee with hypoplastic urethra requires island flap urethroplasty after chordee release because of the bowstring effect of a short urethra.

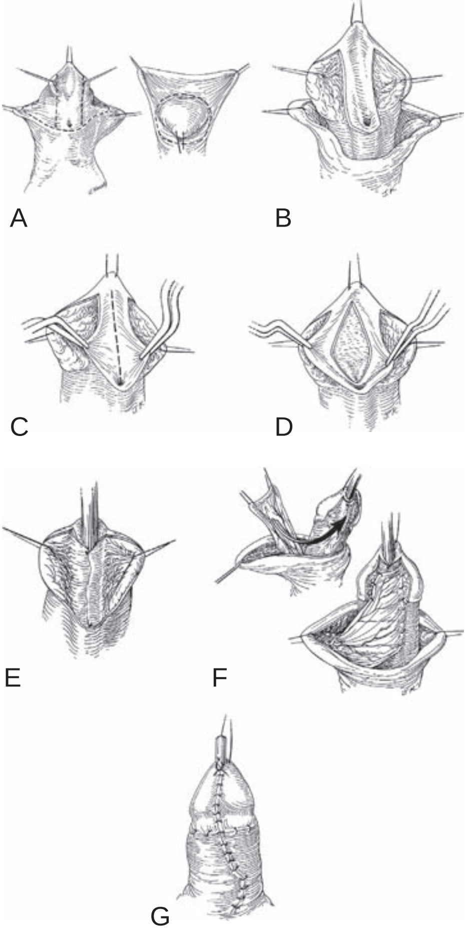


FIGURE 30-12 Tubularized incised plate (TIP) urethroplasty in distal, primary hypospadias repair. **A,** Stay sutures are placed, and proposed urethral plate demarcating and circumferential incisions are marked. **B,** Parallel longitudinal and circumferential incisions have been made. **C,** Proposed longitudinal line of incision in the midline of the urethral plate. **D,** Urethral plate has been incised. **E,** Urethral plate tubularized over a 6-F Silastic catheter with care not to close the distal extent (meatus) of the incised urethral plate too tightly. **F,** Subcutaneous (dartos) tissue flap is harvested from lateral or dorsal penile shaft and repositioned over the neourethra as a second layer of coverage. **G,** Glans penis has been approximated in two layers, redundant skin excised, and indwelling bladder catheter secured. (From Retik AB, Borer JG: Primary and reoperative hypospadias repair with the Snodgrass technique. *World J Urol* 16:186–191, 1998.)

   g. Urinary diversion for 2 weeks in all but very distal repairs, with a small Silastic urethral stent, ensures adequate bladder drainage.
   h. Compressive dressing for 2 to 3 days is commonly used.
5. Results and complications
   a. Small urethrocutaneous fistulae are the most common complication. These may be closed in layers with 90% success.
   b. Postoperative bleeding can usually be stopped with compression.
   c. UTI occurs in less than 10% of cases and can be treated with the usual oral agents.

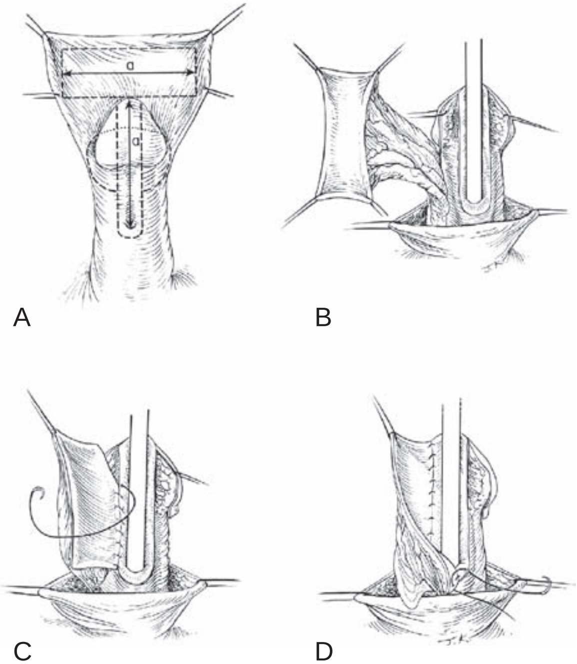


FIGURE 30-13 Onlay island flap repair. **A,** Proposed incisions for urethral plate and preputial skin onlay. **B,** Pedicled preputial skin onlay with stay. **C,** Initial full-thickness suture approximation of onlay flap and urethral plate. **D,** Approximation at proximal extent.

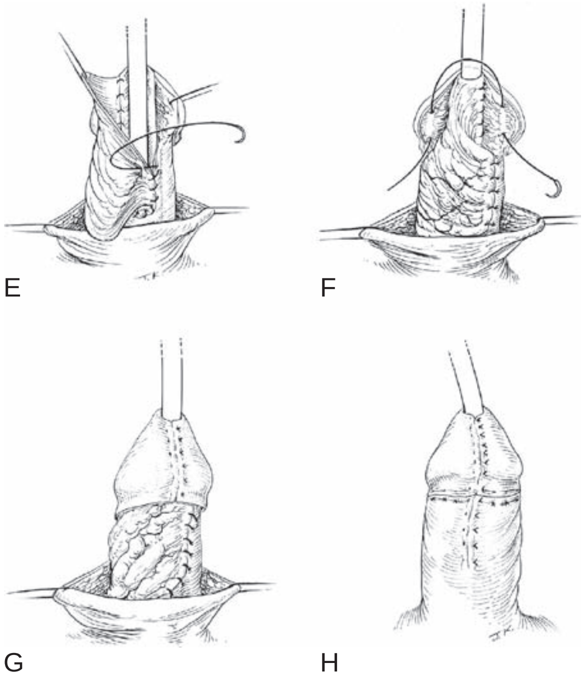


FIGURE 30-13, cont'd **E,** Completion of anastomosis with running subcuticular technique. **F,** Inferolateral border of onlay pedicle has been advanced as a second layer coverage of proximal and longitudinal suture lines. **G,** Approximated glans. **H,** Completed repair. (From Atala A, Retik AB: Hypospadias. In Libertino JA, editor: *Reconstructive urologic surgery,* ed 3, St. Louis, 1998, Mosby.)

d. Strictures are rare and usually occur at the meatus or the proximal end of the repair and are treated by Y-V meatoplasty or excision; direct vision urethrotomy is sometimes successful for short strictures. Severe urethral strictures require additional work, usually a complete "takedown" with incorporation of grafts or flaps to provide additional tissue for repair.
e. When carefully done, the procedures outlined provide a functional and cosmetically nearly normal penis and meatus even in the most severe hypospadias cases.

## CRYPTORCHIDISM

1. Incidence is 1% of boys.
2. Origin: aberrant testicular descent; possible failure of pituitary-gonadal axis in late gestation, that is, absent luteinizing hormone (LH) surge or blunted testicular response
3. Associated findings
   a. **Patent processus vaginalis 90%; symptomatic hernia rarely occurs.**
   b. **Infertility is doubled in untreated unilateral undescended testis and may be as high as 35% in bilateral cryptorchidism. Surgery before age 2 and treatment with an analogue of LH-releasing hormone may improve fertility.**

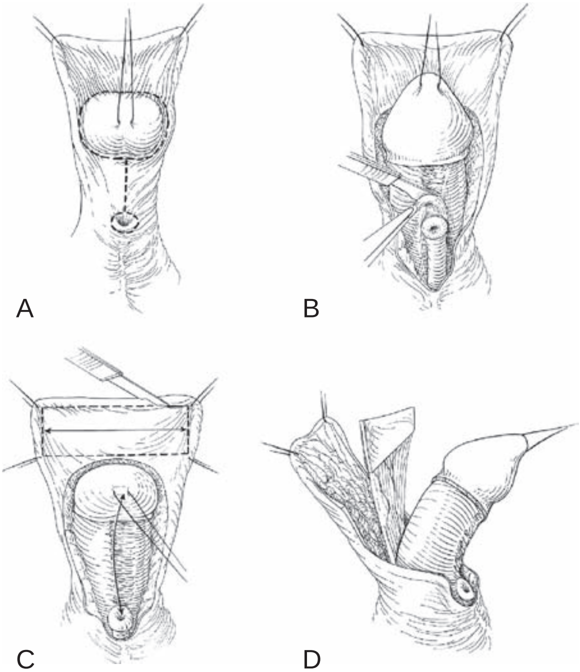


FIGURE 30-14 Transverse preputial island flap repair. **A,** Proposed initial incisions for proximal shaft/penoscrotal hypospadias. **B,** Release of tethering urethral plate and "dropping" of meatus proximally. **C,** Incision of preputial skin of appropriate dimensions for length of defect and width for desired luminal diameter. **D,** Harvested transverse preputial island flap.

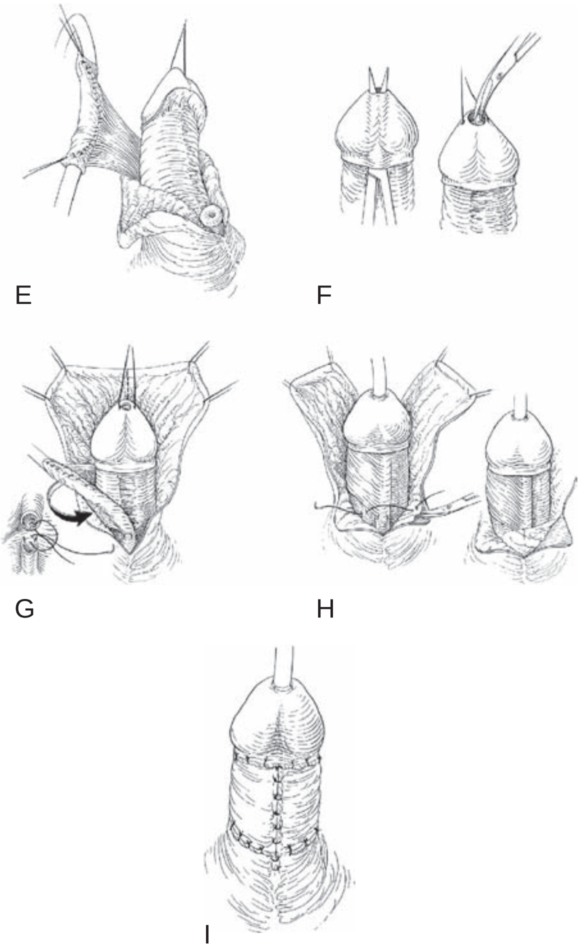


FIGURE 30-14, cont'd **E,** Running subcuticular suture tubularization has been performed over a Silastic catheter to be followed by a second-layer running Lembert suture. **F,** Generous glans channel is fashioned for neourethral passage. A core of glans tissue is excised to achieve sufficient caliber. **G,** Native urethral meatus is fixed to corpora cavernosa prior to performing proximal anastomosis with the neourethra. **H,** Subcutaneous (dartos) tissue coverage of anastomosis. (From Atala A, Retik AB: Hypospadias. In Libertino JA, editor: *Reconstructive urologic surgery,* ed 3, St. Louis, 1998, Mosby.)

   c. **Testicular malignancy is 10 to 100 times more common** than in the general population.
   d. **Undescended testis is part of many syndromes (e.g., prune belly, exstrophy, genetic disorders, intersex states [when associated with even mild hypospadias]).**

4. Diagnosis
   a. Careful examination will discriminate retractile from truly undescended testis in most cases. But in some, a "tethered" or low but undescended testis can only be identified after a period of monitoring while the child grows and the distance between the pubic bone and base of the penis lengthens.
      1) A testis that can be manipulated into the scrotum with a gentle stretch of the cremaster that does not retract into the canal is retractile and requires no surgery.
5. Management
   a. Inguinal exploration at 4 to 6 months of age (spontaneous descent is rare after 3 months)
   b. Most undescended testes are palpable; 85% are canalicular even if impalpable and can be brought down with conventional orchiopexy.
   c. If the canal is empty, the peritoneum is opened; either a testis or blind ending vas deferens and gonadal vessels are found overlying the psoas above the internal inguinal ring. Only identification of the vessels proves testicular absence and constitutes sufficient exploration because the vas may be embryologically separate from the testis.
   d. Fowler-Stephens orchidopexy will bring down an intraabdominal testis by dividing the spermatic vessels. In this case, collateral flow to the testis via the artery to the vas deferens or the vessels running with the cremasteric muscle will provide adequate perfusion in more than 70%.
   e. A testis that cannot be brought into the scrotum should be removed if the contralateral one is normally descended.
6. Results
   a. The Fowler-Stephens procedure, in our experience, has been 70% successful, as judged by palpation of a normal-feeling testis in the scrotum.
   b. Results of conventional orchidopexy are better.

## HERNIA/COMMUNICATING HYDROCELE

1. Incidence is 1% to 4% of mature infants and 13% of premature infants.
2. Origin is failed closure of processus vaginalis after testicular descent or may be associated with incomplete descent.
3. Only associated findings may be frank hernia (sac containing bowel or other organ) or undescended testis.
4. Principle differential diagnosis is with a congenital scrotal hydrocele associated with a closed processus vaginalis. Neonatal scrotal hydroceles are present half the time in infants and will usually be reabsorbed by 12 to 15 months of age. No surgery is required. A communicating hydrocele is suggested by changing the volume of fluid surrounding the testicle. It is important not to confuse contraction of the dartos muscle of the scrotal wall with a change in hydrocele size.
5. Unlike a true hernia, which is repaired promptly in infants because of risk of incarceration, a communicating hydrocele may be fixed electively, usually before the first birthday.

## APPENDAGES

1. Testicular and epididymal appendages are present usually at the upper pole of the testis or epididymis. They represent müllerian or wolffian duct remnants and are only bothersome when torsion of the appendage occurs.
2. **Torsion of the appendix can sometimes be differentiated from testicular torsion by point tenderness and swelling at the upper pole or the "blue dot" sign** in which the infarcted tissue is apparent beneath the scrotal skin as a dark spot. Boys with torsion of the appendix testis may have a visible cremaster reflex. Cremasteric contraction almost never occurs with torsion of the spermatic cord.
3. When doubt exists, along with the risk of spermatic cord, scrotal exploration is essential. If the diagnosis is certain, treatment is symptomatic; pain will usually resolve in 3 to 5 days. If pain persists, transscrotal excision usually results in complete resolution of pain.

# Cloacal Dysgenesis/Persistent Cloaca

## CLOACA ANOMALY

Cloaca anomaly represents failure of the urorectal septum to descend, resulting in a single perineal opening or a sinus into which the rectum, vagina, and urethra enter.

1. The upper urinary tract should be evaluated with ultrasonography. Associated hydronephrosis, often related to hydrocolpos, dysplasia, fusion anomalies, ectopia, **UPJO, and duplication are seen in 33% to 83% of infants with persistent cloaca.** Echocardiography to rule out cardiac anomalies and lumbosacral spine ultrasound or **MRI to assess for tethered spinal cord anomalies and tethering should also be ordered.**
2. Genitosinography, VCUG if possible, and cystovaginoscopy are necessary to assess the anatomy. Diverting colostomy is usually done early, as in an imperforate anus, and this assessment can be performed under the same anesthetic.
3. Reconstruction via a midline posterior approach (Peña-DeVries) is carried out at age 4 to 12 months and consists of:
    a. Rectal tapering and pull through
    b. Combined mobilization of the vagina and urethra as a unit with longitudinal separation of the urogenital sinus for cloacas that are shorter than 3 cm. Longer cloacas may need abdominal and perineal mobilization of the bladder, vagina, and rectum. Clitoroplasty, labioplasty, and vaginoplasty can then follow mobilization.
    c. Spinal anomalies and neurogenic bladders are common.

## VAGINAL ATRESIA AND MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME

1. Hormonal assays can be used to distinguish primary vaginal atresia from a short vagina in girls with testicular feminization. Girls with primary vaginal atresia have normal LH and follicle-stimulating hormone (FSH) levels and low testosterone levels.
    a. Failure of müllerian duct to penetrate the urogenital sinus
    b. Vascular accident
    c. Isolated anomaly
    d. Often presents at puberty with amenorrhea

   e. Two forms:
      1) Distal: Urogenital sinus fails to form the lower portion of the vagina; the uterus, cervix, and upper portion of vagina are normal.
      2) Mullerian: (Mayer-Rokitansky-Küster-Hauser syndrome) See below.
   f. Vaginoplasty is performed using a 10-cm loop of colon, which is reversed and brought to the perineum at the introitus.
2. Rokitansky syndrome
   a. Combination of müllerian duct abnormality, often duplication with vaginal atresia with ipsilateral renal agenesis
   b. Abnormality of the müllerian ducts may be associated with absence of the mesonephric duct because both structures are closely associated during early embryonic differentiation.
   c. It may present in the newborn period with hydrocolpos but commonly presents with amenorrhea or hematocolpos at puberty; it is sometimes discovered during investigation of a solitary kidney.
   d. Those with complete uterovaginal agenesis are managed as primary vaginal atresia; some have normal or septate uteri above the level of obstruction. Girls with uterine obstruction require vaginoplasty.
   e. A special case is the patient with complete uterovaginal duplication and unilateral vaginal atresia.
      1) Because one uterine horn drains normally, these girls have normal menstrual periods, cyclic abdominal pain, and pelvic mass.
      2) These girls may be managed by transvaginal marsupialization, thereby establishing drainage of the obstructed segment or by resection of the blocked segment if the uterus is atrophic.

## CLINICAL PEARLS

1. Most congenital disorders and associated anomalies are predictable if the embryology is known.
2. Understanding the nuances of ureteral duplication and ureteral ectopia helps predict the associated clinical manifestations of each anomaly of the upper urinary tract.
3. Despite lasting commitment to hypospadias repair and numerous approaches to correction, reconstruction of hypospadias and associated chordee remains challenging.

f. Ultrasound is the study of choice for the evaluation of these genital and associated renal anomalies. VCUG is used to evaluate for reflux. Cystovaginoscopy helps to delineate the introital anatomy.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *Discuss the incidence and pathophysiology of kidney fusion anomalies, and give three examples.*
2. *Name three subtypes of cystic abnormalities of the kidneys and their pathophysiologies.*
3. *Discuss the incidence of ureteral duplications, and describe the association with vesicoureteral reflux (VUR) and obstruction.*
4. *Describe the grading system for VUR and why it is important to the practicing urologist.*
5. *Describe anomalies that are associated with hypospadias and create an algorithm for surgical correction of hypospadias depending on the location of the meatus.*

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## CHAPTER 31

# Geriatric Urology

George W. Drach, MD, FACS, FCPP

## Urology and Aging Patients

Our growing geriatric population will impact urology in major ways over the next 2 to 3 decades. General urologists will see in their offices nearly 50% of their patients in the over-65 age group (Table 31-1). Urologists will also face difficult management decisions opting for or against major surgery in these patients. This is especially true for patients with bladder and prostatic cancer because they often do not reach the stage of invasive cancer until over age 60 (Figure 31-1). Some of these surgical candidates remain relatively healthy. Others demonstrate poor surgical risk because of their general condition and comorbidities.

Should we in urology approach these elderly patients differently from our younger, healthier patients? Yes, but the response to this question comes in modification of three elements of our usual "evaluation and management" algorithm: Steps in initial evaluation of the elderly patient differ, decision processes regarding further evaluation and recommendation for treatment require alteration, and decisions on management of definitive therapy require additional thought integrated into the milieu of aging.

Several excellent sources of help exist for geriatric urology. Throughout this chapter I will refer to a small text, *Geriatrics at Your Fingertips* (GAYF), which is of great assistance in management of all geriatric patients. Another source is the text, *Geriatrics Syllabus for Specialists*. Both are available from the American Geriatrics Society, and both should be on the office bookshelf of every urologist who treats adults. In addition, the text *Primer of Geriatric Urology* has recently been published.

To summarize, for our geriatric urology patients, one must alter the initial evaluation to include careful drug history,

TABLE 31-1 **Outpatient Visits by Medicare Patients (2006)**

| Specialty | % |
|---|---|
| Cardiology | 58.4 |
| Ophthalmology | 48.5 |
| Urology | 47.9 |
| General internal medicine | 42.7 |
| General surgery | 35.8 |
| Neurology | 28.6 |
| Dermatology | 28.1 |
| Otolaryngology | 22.5 |
| Orthopedic surgery | 25.0 |
| Family practice | 25.9 |
| Psychiatry | 9.9 |
| Gynecology | 7.1 |

*(Adapted from Drach GW, Forciea MA: Geriatric patient care: basics for urologists,* AUA Update Series *24:286–296, 2005.)*

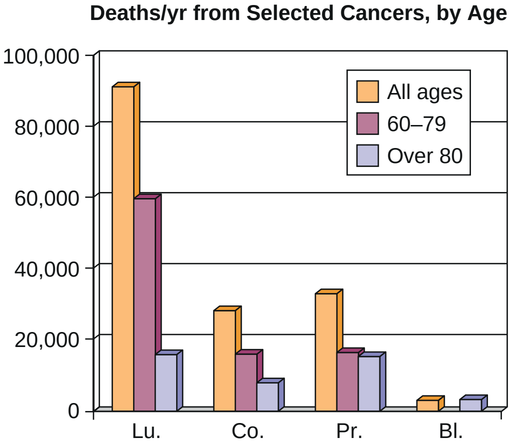

**FIGURE 31-1 Most prostate cancer deaths occur after age 60. Bladder cancer deaths do not become noticeable until after age 80. *Lu,* Lung; *Co,* colon; *Pr,* prostate; *Bl,* bladder.** (Adapted from Hollenbeck BK, Miller DC, Taub D, et al: Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older, *Urology* 64:292–297, 2004.)

obtain necessary old records, and evaluate functional abilities. Therapeutic decisions must be based upon presence or absence of comorbidities along with total functional capacity, rather than chronological age. Finally, the perioperative period must include concern for optimization of comorbidities, attention to pain control, fall prevention, and early discharge planning. All possible steps to prevent or ameliorate mental status change are necessary. With these details accomplished, care of our aged patients will be more beneficial.

## CLINICAL PEARLS

1. At the beginning of your evaluation of the geriatric urology patient, you must assess and integrate the patient's cognitive ability.
2. High functional ability of the older patient predicts a likely successful outcome of your treatment program.
3. Decisions on advising therapeutic intervention must be based on physiologic age, not chronologic age.
4. Discharge planning should begin before any hospital admission and must include the social conditions of the patient.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

# Special Aspects of Approach to the Geriatric Patient

## INITIAL EVALUATION

Of course, one begins with the usual history and physical examination, but several additional inquiries and examinations are needed. A first addition includes **careful attention to the medication regimen and the patient's adherence to it.** Elderly patients often do not take medications as prescribed. They may take only half doses or take daily doses only once weekly. In other cases they may not take the medication at all, perhaps because of excessive expense or their perception of side effects. In addition, one must ask them about their intake of all over-the-counter medications and herbal or other supplements that can affect their health. The average person over age 70 takes four to five prescription medications and two to four supplemental medications. These all must be recorded so that all personnel know what is actually taken.

One risk buried below this medication problem is that one must avoid the routine rewriting on admission of all medications "found in the record." What happens if you order an alpha-blocking agent such as terazosin to a patient who has not in reality taken this prescribed medication? One risks side effects such as postural hypotension and falls. On admission, order only those necessary drugs that the patient actually takes and those needed for procedural preparation (e.g., antibiotics).

Another challenge is the **recovery of information specific to prior treatment.** Older people tend to forget details of treatments received years ago. If the patient has received radiation, what was the total dose and area of the field(s)? If the patient had surgery, what was actually done? Did the prior surgeon take out over four feet of small bowel? Even though chasing down such information can be difficult, it is very necessary.

**Other significant additions to the geriatric evaluation are an assessment of the cognitive, mobility, and flexibility functions.** These three elements can be combined to give an estimate of the patient's overall functional ability. **First,** it is extremely important to develop your own opinion of the patient's mental abilities and to enter that assessment into the record. If the patient seems to be a poor historian or defers the history to a caretaker, perform a simple mental evaluation such as the "mini-cog and clock-drawing" tests (found in *Geriatrics at your fingertips* [GAYF], ed 14, New York, 2012, American Geriatrics Society) and record the results. This determination is very important if you are to obtain informed consent for any medical therapy or surgical procedure. **Second,** if mobility seems limited, do a brief "get up and go" mobility test (again found in GAYF). And **third,** as a component of your physical examination, evaluate the flexibility and strength of the limbs and back. A full ROM of every joint is not needed for adequate function, but severe restrictions will indicate the need for supplemental help and/or rehabilitative services before and after treatment.

All the above contribute to your assessment of the functional capacity of the patient. **No element of your initial geriatric evaluation predicts less risk of postchemotherapy or perioperative morbidity and mortality than a high level of functional ability.** As an example of the importance here, it is wonderful to successfully repair stress urinary incontinence in the older female, but begets a failure if you do not realize that because of limited mobility she cannot get to the bathroom in time to void anyway.

At this point, urologists also must learn of the social status and living capabilities of their patients. Do they live alone (as do more than 50% of females over age 70 in the United States)? Does their home have stairs? Do they have adequate toileting facilities? Do they have adequate heat and air conditioning? Who assists them when necessary? Can they perform fully all the activities of daily living (ADL) and instrumental activities of daily living (IADL) (again see GAYF)? This type of survey will indicate to you whether the patient will need assistance when undergoing chemotherapy or following discharge after surgery.

Another important part of initial evaluation should include your estimate of the nutritional status of the older person. Over 25% of all elderly patients show evidence of malnutrition when first seen. Certain findings hint at such a problem: BMI less than 22, serum albumen less than 3.5, total cholesterol less than 160 mg/dL, and involuntary weight loss of more than 10 pounds in the last 6 months.

## Therapeutic Decisions

At this point, having performed a more global evaluation, one reaches an overall assessment of the health status of the patient. Comorbidities are noted and evaluated also. One then decides to pursue further evaluation and/or treatment based on the physiological health and functional ability rather than an arbitrary chronological age. **This avoids two great errors that can be made in the care of the geriatric patient: withholding adequate care because of chronological age alone or providing overaggressive care in spite of physiological frailty.** This contrast in care becomes evident in decisions about aggressive surgery in treatment of bladder cancer. Such a patient at 78 years of age in reasonable health with only one comorbidity (diabetes mellitus II) can expect to live at least 10 years and can definitely be offered cystectomy and diversion for potential cure. But in order to use this knowledge effectively, the physician must know the brackets of life expectancy for the aged patient (Table 31-2).

Another example of the use of this approach to really help the patient is summarized in Table 31-3, which provides recommendations about administering chemotherapy to elderly patients with advanced cancer. The same recommendations should apply to radical surgical approaches. Most authorities agree that the presence of more than two serious comorbidities (such

TABLE 31-2 **Mean Life Expectancy of the Older Patient (in Years)**

| Present age | 65 | 70 | 75 | 80 | 85 | 90 | 95 | 100 |
|---|---|---|---|---|---|---|---|---|
| ***Men:*** | | | | | | | | |
| White | 16 | 13 | 10 | 7 | 5 | 4 | 3 | 2 |
| Black | 14 | 12 | 9 | 7 | 6 | 4 | 4 | 3 |
| ***Women:*** | | | | | | | | |
| White | 20 | 15 | 12 | 9 | 7 | 5 | 3 | 2 |
| Black | 17 | 14 | 11 | 9 | 6 | 5 | 4 | 3 |

*(From* National Vital Statistics Reports *51:30, 2002.)*

TABLE 31-3 **Geriatric Urology: Oncology and Decisions**

Algorithm: (Treat elderly patients within each group according to their health, functional ability, and degree of comorbidity.)
Group 1: Healthy and fit = Standard treatment
Group 2: Partially dependent and two or fewer comorbidities = Would life expectancy with treatment be better, or could treatment be tolerated?
Group 3: Frail, dependent, three or more comorbidities = Treat palliatively only.

*(Adapted from* Cancer Control: Journal of the Moffitt Cancer Center *8:2–26, 2001.)*

TABLE 31-4 **Decisions Needed in Moving Forward in Elderly Patient's Evaluation**

| | |
|---|---|
| Screening? | PSA, cytology |
| Imaging? | KUB, CT, MRI, ultrasound, other |
| Biopsies? | Prostate, penile, renal, bladder, other |
| Procedures? | Cystoscopy, percutaneous approaches |

as coronary or peripheral artery disease, diabetes mellitus, and chronic obstructive pulmonary disease) should lead one to more conservative treatments in most instances (see Table 31-3). This is especially true when deciding on chemotherapy or radical surgery for urologic malignancies. The decision to administer chemotherapy or surgery to an individual who has a life expectancy of only 2 years seems ludicrous if that person would face a significant risk of complications and death from chemotherapy or surgery alone. On the other hand, chemotherapy, radiotherapy, or even surgery may be clearly indicated for the severely ill patient if it will provide additional comfort and daily functioning (palliation) for the remaining days of the patient's life.

If indeed the geriatric patient appears to have a high degree of health for his or her age, then one proceeds with additional evaluative steps (Table 31-4). The admonition at this point remains the well-known statement: "If you are not likely to treat the patient (or the patient will not accept treatment) even if the test or biopsy is positive, then why do the test or biopsy?" This quandary has become very important in the context of the age at which we should cease PSA screening for prostate cancer. At a conference that I attended in Iowa, the consensus recommendation for cessation of PSA testing after age 75 did NOT include an age limit. Rather, it proposed that PSA testing should continue as long as the patient had an expectation of 5 to 10 years of functionally productive life and would be a candidate for definitive therapy.

## The Perioperative Period

If one decides to proceed with operative treatment of some disease process, then several steps become more important for the geriatric patient.

## PREOPERATIVE PATIENT OPTIMIZATION

These steps include any additional preoperative evaluation and improvement of comorbidities. Experience and literature emphasize that **special attention must be paid to cardiovascular and pulmonary status, renal function, and gastroenteric function.** Our geriatric medicine colleagues may assist with improvement in cardiac and renal functions. If nutrition is inadequate, studies have shown that intense brief measures, such as hyperalimentation seldom have benefit. The best program, if time allows, is that developed for the patient by a dietician, who also monitors compliance in some way over the several months that are needed to improve nutritional status.

A need also exists for **verification of informed consent with comments again on mental capacity of the patient, review or initiation of a living will and advance directives, confirmation of overall functional capacity, analysis of social conditions that will apply on discharge, and early discharge planning.** Because most of these older patients will be covered by Medicare or similar insurance, your plans must include attention to necessary financial constraints. Table 31-5 summarizes approaches to sites for discharge based on Medicare concepts. In addition, a specific additional category exists for those patients needing rehabilitative services.

## PERIOPERATIVE PROBLEMS

Some specific postoperative complications of the elderly require mention. The first regards changes in mentation: delirium, dementia, or depression. **Postoperative delirium is especially common in the elderly and must be a part of the postoperative daily evaluation (see GAYF).**

Secondly, geriatric patients remain at **high risk for falls** while in the hospital. Restraints actually increase this risk and should not be used. Any use of psychiatric medications greatly increases the risk of falls, so they should be avoided. And last, **pain control for the elderly must be managed carefully** with special attention to age-related peculiarities (e.g., meperidine increases risk of seizures).

TABLE 31-5 **Functional Abilities Required for Living Accommodation Level**

| ADL/IADL | Home | Senior Housing | Assisted Living | Nursing Home |
|---|---|---|---|---|
| Mobility | Independent or assisted | Independent or assisted | Independent or assisted | Dependent |
| Toilet | Independent | Independent | Independent | Dependent |
| Chew/swallow | Independent | Independent | Independent | Dependent |
| Dressing | Independent | Independent | Independent | Independent, assisted, or dependent |
| Bathing | Independent | Independent | Independent | Independent, assisted, or dependent |
| Transportation | Independent | Independent | Assisted or dependent | Assisted or dependent |
| Finances | Independent | Independent | Assisted or dependent | Assisted or dependent |
| Telephone | Independent | Independent | Assisted or dependent | Assisted or dependent |
| Shop/cook | Independent | Independent | Assisted or dependent | Dependent |
| Laundry/clean | Independent | Independent | Assisted | Dependent |

*ADL/IADL,* Activities of daily living/instrumental activities of daily living.
*(Adapted from Drach GW, Forciea MA: Geriatric patient care: Basics for urologists,* AUA Update Series *24:286–296, 2005.)*

## *Self-Assessment Questions*

1. *Initial evaluation of the geriatric urology patient requires what three steps in addition to the usual history and physical examination?*
2. *What single factor in the evaluation of the elderly patient gives the best estimate of how the patient will respond to the challenges of chemotherapy or surgery?*
3. *What history, signs, or laboratory findings point to the possibility of poor nutrition in the elderly?*
4. *How do we separate the three groups of the elderly in our algorithm for advising advanced treatment, such as chemotherapy or surgery?*
5. *When performing discharge planning, what elements must be met in order to place the patient into senior housing?*

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## CHAPTER 32

# Venous Thromboembolism in Urology Surgery

Todd E.H. Hecht, MD, FACP, SFHM

## Risk of Venous Thromboembolism in Urology

Venous thromboembolism (VTE) is common in the United States, particularly in surgical populations. The incidence of VTE in the United States has been estimated at approximately 70 to 113/100,000/year, with the consequent estimation of upwards of 200,000 new cases annually. Further, VTE historically has been strongly associated with mortality, with studies estimating a 1-month all-cause mortality rate of 11% after VTE and a 3-month all-cause mortality rate of 17.4% after pulmonary embolism (PE).

The rate of VTE in urological surgery has been variably estimated in the literature. One recent guideline estimated that, without the use of VTE prophylaxis, the rate of deep venous thrombosis (DVT) and PE was 10% and 1%, respectively, in open urological surgery patients. Another guideline estimated the rate of symptomatic VTE to be 1% to 5%. In general, the risk of symptomatic VTE depends on the nature of the procedure, with transurethral procedures carrying a lower risk of VTE than open procedures. In light of this, the most recent American College of Chest Physicians (ACCP) Guidelines on VTE Prevention advocates the use of two risk-scoring systems to quantify the risk of VTE; these scoring systems will be further explored later in this chapter.

## VTE Prophylaxis Methods

A number of options are available for VTE prophylaxis, the supporting evidence for which will be discussed later in this chapter. Pharmacologic options will be discussed first, followed by mechanical forms of prophylaxis.

Unfractionated heparin (UFH) has been used for decades for the prevention of VTE in a variety of surgical and medical populations. UFH acts through several mechanisms, including the binding and activation of antithrombin (AT) with inactivation of various clotting factors. The standard dosing regimen is 5000 units administered subcutaneously three or two times daily. Low molecular-weight heparin (LMWH) has been available clinically for the past 2 to 3 decades; the two formulations available in the United States are enoxaparin (Lovenox) and dalteparin (Fragmin). LMWH exerts its effect predominantly through the inhibition of Factor Xa, and to a lesser degree through the inhibition of Factor IIa, via AT. LMWH has been associated with a lower incidence of heparin-induced thrombocytopenia (HIT) than with UFH,[10] but should be used with caution and only at lower doses in patients with a creatinine clearance less than 30 mL/min or on dialysis. Enoxaparin is typically dosed at 40 mg subcutaneously once daily in nonorthopedic populations; dalteparin is dosed at 5000 units subcutaneously once daily. Fondaparinux (Arixtra) is a synthetic inhibitor of factor Xa which has been studied as a form of VTE prophylaxis in a number of surgical and medical patients. The dose used for prophylaxis is typically 2.5 mg subcutaneously once daily. While a variety of novel oral anticoagulants have recently been approved for either the prevention of embolic complications from atrial fibrillation or the prevention and treatment of VTE, none of these agents has been studied as a form of VTE prophylaxis in nonorthopedic surgical populations, so these agents should not be considered options for urologic patients.

The two major mechanical prophylaxis strategies are intermittent pneumatic compression (IPC) devices and elastic stockings (ES). IPC sleeves are typically applied to the calves and require a power source to operate, though portable battery-operated devices have been developed over the past decade and may be associated with better outcomes than nonportable versions. ES come in both thigh-high and knee-high varieties.

## VTE Prophylaxis Strategies

Primary evidence for VTE prophylaxis in urological surgery is fairly scant. Most trials have either been retrospective or nonrandomized. As a consequence, most guidelines extend their recommendations from other comparable surgical populations such as general surgery and gynecology. Although certain unique urologic populations (e.g., patients undergoing cystoscopic and transurethral procedures) may not be addressed properly using this approach, the paucity of primary urological data compels most guidelines to proceed in this fashion.

**Several guidelines exist to inform the approach for providing VTE prophylaxis in urological surgery patients.** The most widely recognized VTE prophylaxis guidelines are the ACCP Guidelines, which published its ninth edition in 2012. The most extensive guidance for urologic patients in particular is provided by the American Urological Association (AUA) Best Practice Statement for the Prevention of Deep Vein Thrombosis in Patients Undergoing Urologic Surgery. Lastly, the National Clinical Guideline Centre in the UK published the NICE Guidelines on VTE Prophylaxis for all populations in 2010.

**The AUA Guidelines approach their recommendations for VTE prophylaxis by using a different VTE risk model and stratifying patients by type of surgical procedure.** They provide a list of 21 risk factors (Table 32-1) and then propose a VTE risk model (Table 32-2).

The AUA authors then use their risk model to recommend different strategies for patients undergoing different types of procedures. They recommend early ambulation only for the "vast majority of transurethral procedures," except for transurethral resection of the prostate (TURP); they recommend the use of prophylaxis (ES, IPC, or postoperative UFH or LMWH) in patients undergoing TURP who have increased risk of DVT. For patients undergoing antiincontinence and pelvic reconstruction surgery, the AUA authors stratify their recommendations by VTE risk. The authors recommend early ambulation for low-risk patients, use of IPC, UFH, or LMWH for moderate-risk patients, and, for high-risk and highest-risk patients, combination prophylaxis with IPC plus either UFH or LMWH. For patients undergoing laparoscopic or robotic-assisted laparoscopic urologic procedures, the authors recommend IPC during the procedure, and note that high-risk groups that require UFH or LMWH may be identifiable. Lastly, for open urologic procedures, the authors recommend the consideration of combination IPC plus pharmacologic prophylaxis.

**The ACCP Guidelines made a number of new recommendations in their ninth edition that differed somewhat from their prior versions.** In the eighth edition, published in 2008, the authors gave a number of grade 1 recommendations. For patients undergoing transurethral or other low-risk urological procedures, they recommended only early and frequent ambulation without routine use of thromboprophylaxis (grade 1A recommendation). For patients undergoing major, open urologic surgery, they gave a grade 1A recommendation for routine use of thromboprophylaxis. UFH (1B recommendation), ES and/or IPC (1B recommendation), LMWH (1C recommendation), fondaparinux (1C recommendation), and combination pharmacologic and mechanical prophylaxis (1C recommendation) were given fairly strong support. The authors also recommended that mechanical methods be used in patients with active bleeding or at very high risk of bleeding (1A recommendation), with pharmacologic prophylaxis either substituted or added when the bleeding risk subsided (1C recommendation).

**In the ninth edition, the ACCP authors recommended instead that a VTE risk assessment should be performed first to guide whether and what type of prophylaxis should be given. They advocated for two scoring models: the Rogers score derived from data from the Patient Safety in Surgery Study and an adaptation of the Caprini score.**

The Rogers score was developed retrospectively from a database based upon patients who underwent general and vascular surgery (the Patient Safety in Surgery Study). The risk scoring system is presented in Table 32-e1. Based on their derivation data set, the Rogers score authors recommended separating patients into three groups: low VTE risk (score less than 7), medium risk (score 7 to 10), and high risk (score greater than 10). They then validated this scoring system retrospectively in the other half of the database that they used. The risk of VTE found in each data set broken down by Rogers score is shown in Table 32-e2.

The Caprini score is obtained by tallying the number of points based upon an inventory of VTE risk factors, which was modified by the ACCP to that shown in Table 32-e3. The ACCP Guidelines authors then advocated for classifying patients' VTE risk as presented in Table 32-e4. The Caprini score was validated retrospectively in a study of surgical patients published in 2010.

TABLE 32-e1 **Rogers Score Risk-Scoring System**

| *Risk Factor* | *Risk Score Points* |
|---|---|
| **Operation Type Other than Endocrine** | |
| Respiratory and hemic | 9 |
| Thoracoabdominal aneurysm, embolectomy/ thrombectomy, venous reconstruction, and endovascular repair | 7 |
| Aneurysm | 4 |
| Mouth, palate | 4 |
| Stomach, intestines | 4 |
| Integument | 3 |
| Hernia | 2 |
| **ASA Physical Status Classification** | |
| 3, 4, or 5 | 2 |
| 2 | 1 |
| Female gender | 1 |
| **Work RVU** | |
| > 17 | 3 |
| 10-17 | 2 |
| **Two Points for Each of These Conditions** | |
| Disseminated cancer | 2 |
| Chemotherapy for malignancy within 30 days of operation | 2 |
| Preoperative serum sodium > 145 mmol/L | 2 |
| Transfusion > 4 units packed RBCs in 72 hours before operation | 2 |
| Ventilator dependent | 2 |
| **One Point for Each of These Conditions** | |
| Wound class (clean/contaminated) | 1 |
| Preoperative hematocrit ≤ 38% | 1 |
| Preoperative bilirubin > 1.0 mg/dL | 1 |
| Dyspnea | 1 |
| Albumin ≤ 3.5 mg/dL | 1 |
| Emergency | 1 |
| **Zero Points for Each of These Conditions** | |
| ASA physical status class 1 | 0 |
| Work RVU < 10 | 0 |
| Male gender | 0 |

TABLE 32-e2 **Risk of VTE Stratified by Rogers Score**

| | Derivation VTE Rate | Validation VTE Rate |
|---|---|---|
| Low VTE risk (score < 7) | 0.103% | 0.110% |
| Medium VTE risk (score = 7-10) | 0.436% | 0.474% |
| High VTE risk (score >10) | 1.456% | 1.315% |

These authors found that the Caprini score did correlate with the VTE rate and usage of pharmacologic prophylaxis, as shown in Table 32-e5.

The authors of the ACCP Guidelines then provide guidance on usage of prophylaxis for each risk category (with strength of recommendations in parentheses, as shown in Table 32-e6). The authors recommend that LMWH prophylaxis be extended for 4 weeks for high-risk patients undergoing abdominal or pelvic surgery who are not at high risk for major bleeding (1B recommendation). They also give low-strength support for the use of aspirin (2C), fondaparinux (2C), or mechanical prophylaxis alone, with IPC preferred over other mechanical methods (2C) for high VTE risk patients in whom both LMWH and UFH are contraindicated or unavailable.

**Several criticisms can be leveled at the recommendation to use the Rogers and Caprini scores.** The Rogers score authors did not report prophylaxis usage for their data set, so the VTE risk for each group may have actually been higher if prophylaxis had been administered to many of the included patients. Both scores are rather onerous, necessitating the collection of at least 15 risk factors. Further, one of the Rogers score risk factors, the relative value unit (RVU) for the procedure to be performed, may not be readily available to clinicians and may vary over time. Another criticism is that many, if not most, surgical patients will have high scores on each scoring system, which would make the performance of these scores unnecessary. The Rogers score authors found that 71% of their cohort had a Rogers score of 7 or more, which would warrant some form of prophylaxis, with 30% needing pharmacologic prophylaxis. In the validation study of the Caprini score by Bahl et al, the authors found that 52.1% of all patients were assigned to the high-risk category and another 36.5% were in the moderate-risk category, with only 0.9% in the

TABLE 32-e3 **Caprini Score Risk-Scoring System**

| 1-Point Risk Factors | 2-Point Risk Factors | 3-Point Risk Factors | 5-Point Risk Factors |
|---|---|---|---|
| Age 41-60 years | Age 61-74 years | Age ≥ 75 years | Stroke (< 1 month) |
| Minor surgery | Arthroscopic surgery | History of VTE | Elective arthroplasty |
| BMI > 25 kg/m$^2$ | Major open surgery (> 45 minutes) | Family history of VTE | Hip, pelvis, or leg fracture |
| Swollen legs | Laparoscopic surgery (> 45 minutes) | Factor V Leiden | Acute spinal cord injury (< 1 month) |
| Varicose veins | Malignancy | Prothrombin 20210A | |
| Pregnancy/postpartum | Confined to bed (> 72 hours) | Lupus anticoagulant | |
| Unexplained or recurrent spontaneous abortion | Immobilizing plaster cast | Anticardiolipin antibodies | |
| Oral contraceptives or hormone replacement | Central venous access | Elevated serum homocysteine | |
| Sepsis (< 1 month) | | Heparin-induced thrombocytopenia | |
| Serious lung disease, including pneumonia (< 1 month) | | Other congenital or acquired thrombophilia | |
| Abnormal pulmonary function | | | |
| Acute myocardial infarction | | | |
| Congestive heart failure (< 1 month) | | | |
| History of inflammatory bowel disease | | | |
| Medical patient on bed rest | | | |

TABLE 32-e4 **ACCP Guidelines Classification of VTE Risk**

| Caprini Score | Rogers Score | VTE Risk |
|---|---|---|
| 0-1 | < 7 | Very low |
| 2 | 7-10 | Low |
| 3-4 | > 10 | Moderate |
| ≥ 5 | > 10 | High |

TABLE 32-e5 **Correlation of Caprini Score with VTE Rate and Pharmacologic Prophylaxis Usage**

| Caprini Score | VTE Rate | Pharmacologic Prophylaxis Usage |
|---|---|---|
| 0-1 | 0% | 8% |
| 2 | 0.70% | 15% |
| 3-4 | 0.97% | 25% |
| ≥ 5 | 1.94% | 32% |

TABLE 32-e6 **ACCP Guidelines on Use of VTE Prophylaxis by Risk Category**

| VTE Risk | Major Bleeding Risk Not High | Major Bleeding Risk High |
|---|---|---|
| Very low (Rogers < 7, Caprini 0) | Early ambulation | Early ambulation |
| Low (Rogers 7-10, Caprini 1-2) | Mechanical – IPC preferred (2C) | Mechanical – IPC preferred (2C) |
| Moderate (Rogers >10, Caprini 3-4) | LMWH (2B), UFH (2B), or mechanical – IPC preferred (2C) | Mechanical – IPC preferred (2C) |
| High (Rogers >10, Caprini 5) | LMWH or UFH plus mechanical (IPC or ES) | Mechanical – IPC preferred (2C) until pharmacologic agents can be started |

very low-risk category. A risk assessment tool that recommends pharmacologic prophylaxis in over 88% of patients and some form of prophylaxis in all but 1% of patients may be unnecessary as opposed to simply recommending that all surgical patients receive prophylaxis.

TABLE 32-1 **AUA Guidelines on VTE Risk Factors**

| |
|---|
| Surgery |
| Trauma (major or lower extremity) |
| Immobility, paresis |
| Malignancy |
| Cancer therapy (hormonal, chemotherapy, or radiotherapy) |
| Previous venous thromboembolism |
| Increasing age |
| Pregnancy and the postpartum period |
| Estrogen-containing oral contraception or hormone replacement therapy |
| Selective estrogen receptor modulators |
| Acute medical illness |
| Heart or respiratory failure |
| Inflammatory bowel disease |
| Nephrotic syndrome |
| Myeloproliferative disorders |
| Paroxysmal nocturnal hemoglobinuria |
| Obesity |
| Smoking |
| Varicose veins |
| Central venous catheterization |
| Inherited or acquired thrombophilia |

TABLE 32-2 **AUA Guidelines on VTE Risk Model**

| VTE Risk | Patient Characteristics |
|---|---|
| Low | Minor surgery, age < 40, no additional risk factors |
| Moderate | Minor surgery with additional risk factors<br>Surgery in patients aged 40-60 with no additional risk factors |
| High | Surgery in patients aged > 60<br>Surgery in patients aged 40-60 with additional risk factors |
| Highest | Surgery in patients with multiple risk factors |

**The NICE Guidelines are similar to the other two guidelines in that the authors recommend assessing the VTE risk for urological surgery patients prior to prophylaxis.** The NICE Guidelines authors judge a patient to be at risk for VTE if the patient has one or more risk factors for VTE as indicated in Table 32-e7. The authors then recommend the use of mechanical prophylaxis beginning at admission for patients with any of the VTE risk factors listed in Table 32-e7. They include ES and IPC as acceptable options and recommend continuing these until the patient no longer has significantly reduced mobility. The authors go on to recommend the addition of pharmacologic prophylaxis with LMWH or UFH (the latter of these in patients with renal failure) for patients who do not have elevated risk of major bleeding (defined as one or more bleeding risk factors as listed in Table 32-e8) or in whom the risk for VTE exceeds the risk of bleeding. The authors recommend extension of pharmacologic prophylaxis for 28 days postoperatively in patients who have had major cancer surgery in the abdomen or pelvis.

TABLE 32-e7 **NICE Guidelines on VTE Risk Factors**

| |
|---|
| Surgical procedure with a total anesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb |
| Acute surgical admission with inflammatory or intraabdominal condition |
| Expected significant reduction in mobility |
| Active cancer or cancer treatment |
| Age over 60 years |
| Critical care admission |
| Dehydration |
| Known thrombophilias |
| Obesity (BMI > 30 kg/m$^2$) |
| One or more significant medical comorbidities (e.g., heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions) |
| Personal history or a first-degree relative with a history of VTE |
| Use of hormone replacement therapy |
| Use of estrogen-containing contraceptive therapy |
| Varicose veins with phlebitis |

TABLE 32-e8 **NICE Guidelines on Bleeding Risk Factors**

| |
|---|
| Active bleeding |
| Acquired bleeding disorders (such as acute liver failure) |
| Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2) |
| Lumbar puncture, epidural, or spinal anesthesia expected within the next 12 hours |
| Lumbar puncture, epidural, or spinal anesthesia within the previous 4 hours |
| Acute stroke |
| Thrombocytopenia (platelets less than 75,000) |
| Uncontrolled systolic hypertension (230/120 mm Hg or higher) |
| Untreated inherited bleeding disorders (such as hemophilia and von Willebrand disease) |

## Summary

**VTE is a significant risk for patients undergoing urological surgery, though different procedures may carry different risks.** Most guidelines recommend evaluating the risk of VTE through the use of various risk assessment models, though these guidelines do not agree on the type of model used. Further, the recommended models have a number of limitations, including a degree of both cumbersomeness (all require collection of at least 15 variables) and futility (most surgical patients will be identified as *at risk*). **Most guidelines recommend use of pharmacologic prophylaxis with UFH, LMWH, or fondaparinux in higher VTE risk patients, provided the VTE risk outweighs the bleeding risk. In patients with high bleeding and VTE risk, most guidelines advocate for use of mechanical prophylaxis, with IPC being preferred by some guidelines over ES.** All guidelines recommend at least consideration of combination pharmacologic and mechanical prophylaxis in the highest VTE risk patients, provided the bleeding risk is not high. **Extension of LMWH prophylaxis for 28 days is commonly recommended for patients undergoing major cancer surgery in the abdomen and pelvis.**

### CLINICAL PEARLS

1. Venous thromboembolism (VTE) is common after urological surgery without proper use of prophylaxis.
2. Risk of VTE varies by type of procedure and by presence or absence of a number of risk factors.
3. Pharmacologic prophylaxis is generally preferred for patients with both high VTE risk and low bleeding risk.
4. Combination prophylaxis with pharmacologic and mechanical methods should be considered for urological surgery patients with multiple VTE risk factors undergoing major surgery.
5. Prophylaxis with low-molecular-weight heparin (LMWH) should be extended for 4 weeks in patients who are undergoing major abdominal or pelvic surgery for cancer.

**Additional content, including Self-Assessment Questions and Suggested Readings, may be accessed at www.ExpertConsult.com.**

## *Self-Assessment Questions*

1. *What clinical factors have generally been associated with risk for venous thromboembolism (VTE) in surgical patients?*
2. *What types of prophylaxis options are available to reduce the risk for VTE in urological surgery patients?*
3. *How is the type of urological surgery associated with VTE risk?*
4. *Which clinical factors are important in choosing the prophylactic modality?*
5. *How long after major surgery for abdominal or pelvic cancer should LMWH prophylaxis be ideally administered?*

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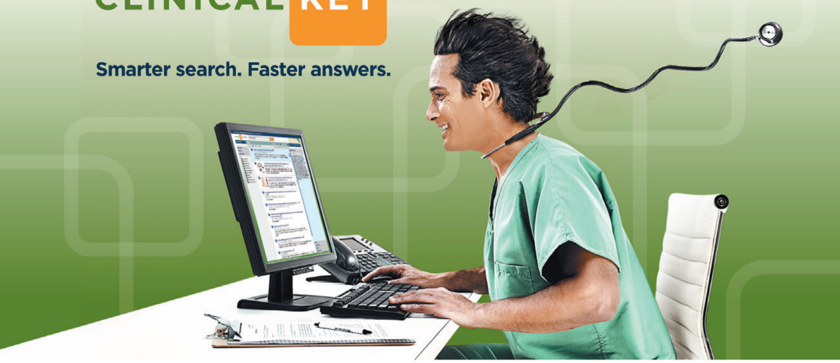

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